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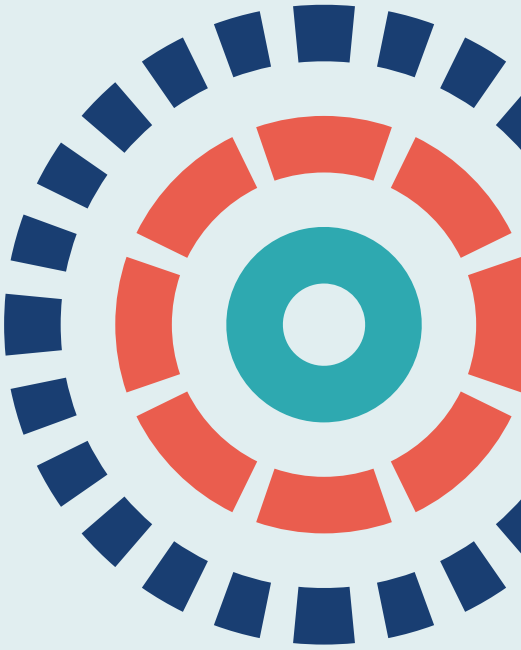

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Selective internal radiation therapies for unresectable early-, intermediate- or advanced-stage hepatocellular carcinoma: systematic review, network meta-analysis and economic evaluation

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This report

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Abstract

Selective internal radiation therapies for unresectable early-, intermediate- or advanced-stage hepatocellular carcinoma: systematic review, network meta-analysis and economic evaluation

Matthew Walton,[1] Ros Wade,[1*] Lindsay Claxton,[1] Sahar Sharif-Hurst,[1] Melissa Harden,[1] Jai Patel,[2] Ian Rowe,[2] Robert Hodgson[1] and Alison Eastwood[1]

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Background: Hepatocellular carcinoma is the most common type of primary liver cancer. Treatment choice is dependent on underlying liver dysfunction and cancer stage. Treatment options include conventional transarterial therapies for patients with intermediate-stage disease and systemic therapy [e.g. sorafenib (Nexavar®; Bayer plc, Leverkusen, Germany)] for patients with advanced-stage disease. Selective internal radiation therapies deliver radiation to liver tumours via microspheres that are injected into the hepatic artery. There are three selective internal radiation therapies: TheraSphere™ [BTG Ltd, London, UK (now Boston Scientific, Marlborough, MA, USA)], SIR-Spheres® (Sirtex Medical Ltd, Woburn, MA, USA) and QuiremSpheres® (Quirem Medical BV, Deventer, the Netherlands).

Objective: To assess the clinical effectiveness and cost-effectiveness of selective internal radiation therapies for treating patients with unresectable early-, intermediate- or advanced-stage hepatocellular carcinoma.

Methods: A search was undertaken to identify clinical effectiveness literature relating to selective internal radiation therapies and relevant comparators for the treatment of hepatocellular carcinoma. Studies were critically appraised and summarised. The network of evidence was mapped to estimate the relative effectiveness of the different selective internal radiation therapies and comparator treatments. An economic analysis evaluated the cost-effectiveness.

Results: Twenty studies were included in the clinical effectiveness review. Two large randomised controlled trials rated as having a low risk of bias [SARAH: Vilgrain V, Pereira H, Assenat E, Guiu B, Ilonca AD, Pageaux GP, *et al.* Efficacy and safety of selective internal radiotherapy with yttrium-90 resin microspheres compared with sorafenib in locally advanced and inoperable hepatocellular carcinoma (SARAH): an open-label randomised controlled Phase 3 trial. *Lancet Oncol* 2017;**18**:1624–36; and SIRveNIB: Chow PKH, Gandhi M, Tan SB, Khin MW, Khasbazar A, Ong J, *et al.* SIRveNIB: selective internal radiation therapy versus sorafenib in Asia-Pacific patients with hepatocellular carcinoma. *J Clin Oncol* 2018;**36**:1913–21] found no significant difference in overall survival or progression-free survival between SIR-Spheres and sorafenib (systemic therapy) in an advanced population, despite greater tumour response in the SIR-Spheres arm of both trials. There were some concerns regarding generalisability of the SARAH and SIRveNIB trials to UK practice. All other studies of SIR-Spheres, TheraSphere or QuiremSpheres were either rated as being at a high risk of bias or caused some concerns regarding bias. A network meta-analysis was conducted in adults with unresectable hepatocellular

carcinoma who had Child–Pugh class A liver cirrhosis and were ineligible for conventional transarterial therapies. The analysis included the SARAH and SIRveNIB trials as well as a trial comparing lenvatinib (Kisplyx®; Eisai Ltd, Tokyo, Japan) (systemic therapy) with sorafenib. There were no meaningful differences in overall survival between any of the treatments. The base-case economic analysis suggested that TheraSphere may be cost-saving relative to both SIR-Spheres and QuiremSpheres. However, incremental cost differences between TheraSphere and SIR-Spheres were small. In a fully incremental analysis, which included confidential Patient Access Scheme discounts, lenvatinib was the most cost-effective treatment and dominated all selective internal radiation therapies. In pairwise comparisons of sorafenib with each selective internal radiation therapy, sorafenib also dominated all selective internal radiation therapies.

Limitations: The existing evidence cannot provide decision-makers with clear guidance on the comparative effectiveness of treatments in early- and intermediate-stage hepatocellular carcinoma or on the efficacy of TheraSphere or QuiremSpheres.

Conclusions: In the advanced-stage hepatocellular carcinoma population, two large randomised trials have shown that SIR-Spheres have similar clinical effectiveness to sorafenib. None of the selective internal radiation therapies was cost-effective, being more costly and less effective than lenvatinib, both at list price and with Patient Access Scheme discounts.

Future work: Future studies may wish to include early- and intermediate-stage hepatocellular carcinoma patients and the low tumour burden/albumin–bilirubin 1 subgroup of advanced-stage patients. Future high-quality studies evaluating alternative selective internal radiation therapies would be beneficial.

Study registration: This study is registered as PROSPERO CRD42019128383.

Funding: This project was funded by the National Institute for Health Research (NIHR) Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 24, No. 48. See the NIHR Journals Library website for further project information.

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Glossary

Adverse effect An adverse outcome that occurs during or after exposure to a drug or other intervention and that may or may not be caused by the intervention.

Assessment Group An independent academic group commissioned by the National Institute for Health Research on behalf of the National Institute for Health and Care Excellence to appraise the clinical effectiveness and cost-effectiveness of selective internal radiation therapies.

Confidence interval A measure of uncertainty around the results of a statistical analysis that describes the range of values within which we can be reasonably sure that the true effect lies. For example, a 95% confidence interval is based on the notion that if a study were repeated many times in other samples from the same population, 95% of the confidence intervals from those studies would include the true value of the effect being measured. Wider intervals indicate lower precision; narrow intervals indicate greater precision.

Conventional transarterial therapies Includes transarterial chemoembolisation, drug-eluting bead transarterial chemoembolisation and transarterial embolisation without chemotherapy. All three forms of conventional transarterial therapy work by administering an embolising agent into the hepatic artery to block blood vessels feeding the tumours in the liver. In the case of transarterial chemoembolisation, also known as conventional transarterial chemoembolisation, Lipiodol® (Guerbet, Villepinte, France) is combined with a chemotherapy agent, typically doxorubicin or cisplatin, which is administered directly to the tumour. In drug-eluting bead transarterial chemoembolisation, drug-eluting beads typically bound with doxorubicin or epirubicin are administered to the tumour via the hepatic artery. Transarterial embolisation, or bland transarterial chemoembolisation, involves only the physical occlusion of blood vessels, with no addition of chemotherapy.

Cost–benefit analysis An economic analysis that converts the effects or consequences of interventions into the same monetary terms as the costs and compares them using a measure of net benefit or a cost–benefit ratio.

Cost-effectiveness acceptability curve A graph describing the impact of uncertainty on the result of a cost-effectiveness model. The graph plots a range of cost-effectiveness thresholds on the horizontal axis against the probability that the intervention will be cost-effective at that threshold on the vertical axis. It can usually be drawn directly from the results of a probabilistic sensitivity analysis.

Cost-effectiveness analysis A type of economic analysis that compares the relative costs and outcomes (effects) of different courses of action. It compares an intervention with another intervention (s) (or the current standard of care) by estimating how much it costs to gain a unit of a health outcome, such as a life-year gained or a death prevented.

Cost-effectiveness model A cost-effectiveness or decision model seeks to answer questions about how to deploy resources in a health-care system. A model is a simplified representation of a real-world condition and treatment pathway, which aims to estimate the costs and consequences arising from making a particular policy decision (i.e. whether or not the NHS should fund a new procedure or drug). All relevant alternative courses of action and their long-term costs and consequences are compared to inform a decision on which option to adopt.

Cost-effectiveness threshold This represents the maximum amount a health-care system is willing to pay to provide a new technology or intervention. National Institute for Health and Care Excellence guidance typically considers interventions with an incremental cost-effectiveness ratio of between £20,000 and £30,000 per quality-adjusted life-year to be cost-effective.

Cost–utility analysis The same as a cost-effectiveness analysis, but the effects or consequences of interventions are expressed in generic units of health gain, usually quality-adjusted life-years.

Credible interval In Bayesian statistics, a credible interval is a posterior probability interval estimation that incorporates problem-specific contextual information from the prior distribution. Credible intervals are used for the purposes similar to those of confidence intervals in frequentist statistics.

Cycle The time horizon in a model is split into cycles that represent the smallest period of time measured in the economic model.

Deterministic sensitivity analysis Explores the impact on model results of varying one or two input parameters at a time.

Dominance In the field of health economics, a treatment option is said to be 'dominant' when it both is less costly and produces better health outcomes than the comparator strategy. Thus, a treatment that both is more expensive and results in poorer health outcomes is referred to as 'dominated'.

EuroQol-5 Dimensions A generic measurement of quality of life used in many clinical trials. This instrument is easy to use and has been extensively validated across many disease areas. The benefit of the EuroQol-5 Dimensions is the availability of utility scores (generated through large population surveys) for each possible combination of questionnaire responses; these can be combined with the time individuals reside in particular health states to calculate the quality-adjusted life-years associated with an intervention.

Fixed-effect model A statistical model that stipulates that the units under analysis (e.g. people in a trial or study in a meta-analysis) are the ones of interest and, thus, constitute the entire population of units. Only within-study variation is taken to influence the uncertainty of results (as reflected in the confidence interval) of a meta-analysis using a fixed-effect model.

Heterogeneity In systematic reviews, heterogeneity refers to variability, or differences, between studies in the estimates of effects. A distinction is sometimes made between 'statistical heterogeneity' (differences in the reported effects), 'methodological heterogeneity' (differences in study design) and 'clinical heterogeneity' (differences between studies in key characteristics of the participants, interventions or outcome measures).

Incremental cost-effectiveness ratio A measure that represents the economic value of an intervention compared with an alternative; it is generally the primary outcome of an economic evaluation. It is calculated by dividing the difference in costs between two interventions by the difference in quality-adjusted life-years. It is the cost of generating an additional quality-adjusted life-year using the intervention we are interested in versus an alternative (usually current clinical practice).

Intention-to-treat analysis An analysis in which all participants enrolled in a trial are analysed according to the intervention to which they were initially allocated, regardless of whether they went on to receive it or not.

Network meta-analysis A meta-analysis in which three or more treatments are compared using both direct comparisons of interventions within trials and indirect comparisons across trials, based on a common comparator.

Probabilistic sensitivity analysis Assesses the joint uncertainty across all input parameters in the model. This is carried out by assigning probability distributions to each input parameter and making random draws from each of these distributions. This process is then repeated many thousands of times, resulting in a distribution of outputs that describe the uncertainty in the results of the model.

Quality-adjusted life-year An index of health gain where survival duration is weighted or adjusted according to the patient's quality of life over the time they are alive. Quality-adjusted life-years are based on utilities, which are valuations of quality of life measured on a scale between full health (1) and death (0). These valuations are multiplied by the number of years that an individual spends in a health state with that particular utility score, and the quality-adjusted life-years are summed over the modelled time horizon.

Quality of life A broad concept incorporating all of the factors that might have an impact on an individual's physical, mental and social well-being. Health-related quality of life refers to the specific impact that a medical condition or treatment has on an individual's functioning and general well-being. Health-related quality of life is generally measured in clinical trials alongside other outcomes to assess the impact of an intervention from a patient's perspective, typically using questionnaires completed by patients, their families or clinicians, such as the EuroQol-5 Dimensions.

Random-effects model A statistical model sometimes used in meta-analysis in which both within-study sampling error (variance) and between-study variation are included in the assessment of the uncertainty (confidence interval) of the results of a meta-analysis.

Randomised controlled trial An experiment in which investigators randomly allocate eligible people into groups that are each assigned a different intervention in order to compare their relative effectiveness and safety.

Relative risk (synonym: risk ratio) The ratio of risk in the intervention group to the risk in the control group. The risk (proportion, probability or rate) is the ratio of people with an event in a group to the total number in the group. A relative risk of 1 indicates no difference between comparison groups. For undesirable outcomes, a relative risk of < 1 indicates that the intervention was effective in reducing the risk of that outcome.

Scenario analysis A process of exploring alternative future outcomes by selection of different assumptions used in the economic model. Scenarios can represent outcomes ranging from optimistic (where input variables are changed to their most optimistic value) to pessimistic (where they are changed to their most pessimistic). These types of analyses test the cost-effectiveness and safety of an intervention in the best and worst cases, and in other plausible 'alternative worlds'.

Statistical significance A result is described as statistically significant when the reported *p*-value falls below the selected significance level; this value represents the probability that the observed result could have occurred owing of chance alone if the 'null hypothesis' is true (i.e. there was no true difference between the groups).

Time horizon The time horizon of an economic model is the duration over which costs and health outcomes are calculated. The choice of time horizon is important, and generally depends on the nature of the condition for which an intervention is being assessed. A long time horizon is preferred in chronic or long-term conditions for which there are likely to be important ongoing management costs and consequences well into the future. The use of a long-term time horizon often involves the extrapolation of short-term data into the future and the use of assumptions about the persistence of treatment effects due to a lack of long-term data.

List of abbreviations

AE	adverse event
AG	Assessment Group
AIC	Akaike information criterion
ALBI	albumin–bilirubin
BCLC	Barcelona Clinic Liver Cancer
BIC	Bayesian information criterion
BNF	*British National Formulary*
BSC	best supportive care
CADTH	Canadian Agency for Drugs and Technologies in Health
CE	Conformité Européenne
CEAC	cost-effectiveness acceptability curve
CEAF	cost-effectiveness acceptability frontier
CI	confidence interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CIRT	Cardiovascular and Interventional Radiological Society of Europe Registry for SIR-Spheres Therapy
CMA	cost-minimisation analysis
CRD	Centre for Reviews and Dissemination
CrI	credible interval
CT	computerised tomography
cTACE	conventional transarterial chemoembolisation
CTT	conventional transarterial therapy
DEB-TACE	drug-eluting bead transarterial chemoembolisation
DIC	deviance information criterion
DSA	deterministic sensitivity analysis
DSU	Decision Support Unit
EASL	European Association for the Study of the Liver
ECOG	Eastern Cooperative Oncology Group
eMIT	electronic market information tool
ENRY	European Network on Radioembolisation with Yttrium-90 Resin Microspheres
EORTC QLQ	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
EQ-5D	EuroQol-5 Dimensions
EQ-5D-3L	EuroQol-5 Dimensions, three-level version
FACT-Hep	Functional Assessment of Cancer Therapy Hepatobiliary-Pancreatic Symptom Index
GP	general practitioner
HCC	hepatocellular carcinoma
HRG	Healthcare Resource Group
HR	hazard ratio
HRQoL	health-related quality of life
HTA	Health Technology Assessment
ICER	incremental cost-effectiveness ratio
INR	international normalised ratio
IPD	individual patient data
ITT	intention to treat
KM	Kaplan–Meier
LYG	life-years gained
MAA	macroaggregated albumin
MELD	Model for End-Stage Liver Disease
MeSH	medical subject heading
MRI	magnetic resonance imaging
MVI	macroscopic vascular invasion
NHS EED	NHS Economic Evaluation Database
NICE	National Institute for Health and Care Excellence

NMA	network meta-analysis
NMB	net monetary benefit
OS	overall survival
PAS	Patient Access Scheme
PFS	progression-free survival
PLLA	poly-L-lactic acid
PREMIERE	Prospective Randomized study of chEmoeMbolization versus radIoEmbolization for the tReatment of hEpatocellular carcinoma
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	international prospective register of systematic reviews
PSA	probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
PVI	portal vein invasion
PVT	portal vein thrombosis
QALY	quality-adjusted life-year
RCT	randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
REILD	radioembolisation-induced liver disease
SARAH	SorAfenib versus Radioembolization in Advanced Hepatocellular Carcinoma
SD	standard deviation
SIRT	selective internal radiation therapy
SIRveNIB	Selective Internal Radiation Therapy Versus Sorafenib in Locally Advanced Hepatocellular Carcinoma
SmPC	summary of product characteristics
SPECT	single-photon emission computerised tomography
TA	technology appraisal
TACE	transarterial chemoembolisation
TAE	transarterial embolisation
TARE	transarterial radioembolisation
TRAE	treatment-related adverse event
TTP	time to progression
WHO	World Health Organization
WTP	willingness to pay

Note

This monograph is based on the Technology Assessment Report produced for NICE. The full report contained a considerable number of data that were deemed confidential. The full report was used by the Appraisal Committee at NICE in its deliberations. The full report with each piece of confidential data removed and replaced by the statement 'confidential information (or data) removed' is available on the NICE website: www.nice.org.uk.

The present monograph presents as full a version of the report as is possible while retaining readability, but some sections, sentences, tables and figures have been removed. Readers should bear in mind that the discussion, conclusions and implications for practice and research are based on all the data considered in the original full NICE report.

Plain English summary

Hepatocellular carcinoma is the most common type of liver cancer. The choice of treatment depends on the extent of the cancer and liver function. Selective internal radiation therapies deliver radiation directly to liver tumours via tiny beads injected into the main blood vessel into the liver. There are three selective internal radiation therapies: TheraSphere™ [BTG Ltd, London, UK (now Boston Scientific, Marlborough, MA, USA)], SIR-Spheres® (Sirtex Medical Ltd, Woburn, MA, USA) and QuiremSpheres® (Quirem Medical BV, Deventer, the Netherlands).

Our aim was to assess the clinical effectiveness of selective internal radiation therapies for patients with hepatocellular carcinoma that is not treatable by surgery, and to assess whether or not these therapies represent good value for money.

There was no meaningful difference between SIR-Spheres and sorafenib (Nexavar®; Bayer plc, Leverkusen, Germany), which is a cancer drug for advanced hepatocellular carcinoma. Studies of other selective internal radiation therapies and studies in patients with less advanced disease were generally of poor quality, so their results may not be reliable. We could not assess whether or not selective internal radiation therapies are beneficial to patients with early- or intermediate-stage hepatocellular carcinoma, or whether or not TheraSphere and QuiremSpheres are beneficial.

Compared with sorafenib or lenvatinib (Kisplyx®; Eisai Ltd, Tokyo, Japan) (another systemic cancer drug), none of the selective internal radiation therapies were good value for money for treating patients with advanced hepatocellular carcinoma. We found that TheraSphere might be cheaper than SIR-Spheres and QuiremSpheres, but differences between TheraSphere and SIR-Spheres were small.

There was not enough evidence for patients with early or intermediate disease to say whether or not selective internal radiation therapy is good value for treating these patients. Future studies in these populations, alongside any studies comparing the selective internal radiation therapies against each other, would be helpful.

Scientific summary

Background

Liver cancer is the fifth most common cancer and the second most frequent cause of cancer-related death globally. Hepatocellular carcinoma is the most common type of liver cancer.

Clinical management of hepatocellular carcinoma is complex; there is a range of treatment options available. The Barcelona Clinic Liver Cancer staging system is used to establish prognosis and enable the selection of appropriate treatment based on underlying liver dysfunction and cancer stage. Treatment options include surgery or ablation for early-stage disease, conventional transarterial therapies for intermediate-stage disease and systemic therapy for advanced-stage disease. Best supportive care is offered to patients when conventional transarterial therapy or systemic therapy is not available or appropriate, including patients with terminal-stage disease.

Selective internal radiation therapies deliver radiation to liver tumours via microspheres that are injected into the hepatic artery. There are three selective internal radiation therapies: TheraSphere™ [BTG Ltd, London, UK (now Boston Scientific, Marlborough, MA, USA)], SIR-Spheres® (Sirtex Medical Ltd, Woburn, MA, USA) and QuiremSpheres® (Quirem Medical BV, Deventer, the Netherlands).

Objective

To assess the clinical effectiveness and cost-effectiveness of selective internal radiation therapies for unresectable early-, intermediate- or advanced-stage hepatocellular carcinoma.

Methods

Methods of the clinical effectiveness review

A comprehensive search was undertaken to systematically identify clinical effectiveness literature relating to TheraSphere, SIR-Spheres and QuiremSpheres compared with each other, conventional transarterial therapy or established clinical management without selective internal radiation therapy, in patients with hepatocellular carcinoma. Randomised controlled trials were eligible for inclusion. Where randomised controlled trial evidence was insufficient to address the decision problem, non-randomised comparative studies and non-comparative studies were considered. In addition, a search for randomised controlled trials of comparator therapies was undertaken to strengthen the network of evidence.

Methods of network meta-analysis

A network meta-analysis was undertaken to estimate the relative effectiveness of the different treatments. Three network meta-analysis models were produced for the different populations of unresectable hepatocellular carcinoma patients: patients eligible for a transplant, patients ineligible for a transplant but eligible for conventional transarterial therapy and patients ineligible for conventional transarterial therapy.

The network meta-analysis in patients eligible for a transplant was not conducted. Clinical advice confirmed that there are short transplant waiting times in the UK, whereas these were much longer in the network trials. Therefore, the network may not be generalisable to UK practice. The network meta-analysis of patients eligible for conventional transarterial therapy was also not conducted because of the lack of good-quality evidence in this population.

Several network meta-analyses of patients who are ineligible for conventional transarterial therapy were conducted for both overall survival and progression-free survival outcomes in the per-protocol and intention-to-treat populations.

Methods of economic modelling

Owing to the limited clinical evidence in the early and intermediate patient groups, the focus of the Assessment Group's economic analysis was on an advanced hepatocellular carcinoma population, in which high-quality randomised controlled trial evidence was available.

The Assessment Group built a fully probabilistic de novo model, which compared the three selective internal radiation therapy treatments with the systemic therapies lenvatinib (Kisplyx®; Eisai Ltd, Tokyo, Japan) and sorafenib (Nexavar®; Bayer plc, Leverkusen, Germany). The model structure comprised a decision tree representing the outcome of the work-up procedure transitioning into a three-state partitioned survival model. The main model structure is similar to that adopted in previous appraisals in advanced hepatocellular carcinoma, consisting of health states representing progression-free survival, post progression and death. The time horizon was 10 years. Costs and benefits were discounted at a rate of 3.5% per annum. Costs were valued at 2017/18 prices.

The model drew on data from the SorAfenib versus Radioembolization in Advanced Hepatocellular Carcinoma (SARAH) [Vilgrain V, Pereira H, Assenat E, Guiu B, Ilonca AD, Pageaux GP, *et al.* Efficacy and safety of selective internal radiotherapy with yttrium-90 resin microspheres compared with sorafenib in locally advanced and inoperable hepatocellular carcinoma (SARAH): an open-label randomised controlled Phase 3 trial. *Lancet Oncol* 2017;**18**:1624–36] and Selective Internal Radiation Therapy Versus Sorafenib in Locally Advanced Hepatocellular Carcinoma (SIRveNIB) (Chow PKH, Gandhi M, Tan SB, Khin MW, Khasbazar A, Ong J, *et al.* SIRveNIB: selective internal radiation therapy versus sorafenib in Asia-Pacific patients with hepatocellular carcinoma. *J Clin Oncol* 2018;**36**:1913–21) trials to estimate the relative effectiveness of selective internal radiation therapy and sorafenib; the base case assumed equivalence in efficacy for all selective internal radiation therapies. A hazard ratio derived from the network meta-analysis was applied to the sorafenib survival curve to estimate the efficacy of lenvatinib. Health state utilities were derived from the per-protocol subgroup of the SARAH trial for selective internal radiation therapy and systemic therapy patients. Resource use and cost inputs were derived primarily from the included trials, targeted literature searches, estimates presented in the companies' evidence submissions, and previous National Institute for Health and Care Excellence technology appraisals.

Confidential Patient Access Schemes are available for a number of modelled technologies, including the comparator therapies lenvatinib and sorafenib and also for QuiremScout® (Quirem Medical BV). All results in this report are based on list prices; separate analyses that include relevant Patient Access Scheme discounts are presented in *Appendix 17*.

Results were presented in terms of incremental net monetary benefit versus the least costly option in each scenario. Fully incremental cost-effectiveness ratios were also produced. Uncertainty was accounted for using probabilistic and deterministic sensitivity analyses. The base case was based on 20,000 model iterations using Monte Carlo sampling methods.

Results

Results of the clinical effectiveness review

Seven randomised controlled trials, seven prospective comparative studies, five retrospective comparative studies and one non-comparative case series were included in the review of clinical effectiveness.

Efficacy and safety of SIR-Spheres

Two large randomised controlled trials rated as being at a low risk of bias (SARAH and SIRveNIB) found no significant difference in overall survival or progression-free survival between SIR-Spheres and sorafenib, despite a statistically significantly greater tumour response rate in the SIR-Spheres arm of both trials (SARAH: 19% vs. 12%, $p = 0.0421$; SIRveNIB: 16.5% vs. 1.7%, $p < 0.001$). The SARAH trial reported a significant difference between groups in health-related quality of life, favouring SIR-Spheres; however, the proportion of patients who completed the questionnaires was low. There was no significant difference in health-related quality of life between groups in the SIRveNIB trial. Adverse events, particularly grade ≥ 3 events, were more frequent in the sorafenib group in both trials.

The Sirtex Medical Ltd (hereafter Sirtex) company submission selected a subgroup of patients from the SARAH trial with $\leq 25\%$ tumour burden and albumin–bilirubin 1 for its base-case analysis in the economic model; this is not a clinically recognised subgroup and was based on a post hoc analysis.

There were methodological differences between the trials; most notably, SARAH was conducted in France, whereas SIRveNIB was conducted in the Asia-Pacific region. Hepatocellular carcinoma in European patients is more likely to be caused by alcohol or hepatitis C, whereas in Asia it is more likely to be caused by hepatitis B. This has implications for the generalisability of the SIRveNIB trial results to the UK population, because the natural history of the disease and treatment options differ. In addition, the SARAH trial included patients with a poor prognosis who would be considered only for best supportive care in UK practice.

Three other randomised controlled trials of SIR-Spheres were included, comparing SIR-Spheres with transarterial chemoembolisation, or drug-eluting bead transarterial chemoembolisation and SIR-Spheres followed by sorafenib with sorafenib alone. Each of these small randomised controlled trials either were rated as being at a high risk of bias or caused some concerns regarding bias. The trials comparing SIR-Spheres with transarterial chemoembolisation or drug-eluting bead transarterial chemoembolisation appeared to favour conventional transarterial therapy over selective internal radiation therapy in terms of survival outcomes. The addition of SIR-Spheres to sorafenib did not appear to increase the number of treatment-emergent adverse events.

Efficacy and safety of TheraSphere

There were two small randomised controlled trials and seven prospective comparative studies of TheraSphere. One of the randomised controlled trials [Prospective Randomized study of chEmoeMbolization versus radIoEmbolization for the tReatment of hEpatocellular carcinoma (PREMIERE): Salem R, Gordon AC, Mouli S, Hickey R, Kallini J, Gabr A, *et al.* Y90 radioembolization significantly prolongs time to progression compared with chemoembolization in patients with hepatocellular carcinoma. *Gastroenterology* 2016;**151**:1155–63.e2] and all of the non-randomised controlled trial studies were rated as being at a high risk of bias, and the other randomised controlled trial caused some concerns regarding bias. PREMIERE compared TheraSphere with transarterial chemoembolisation as a bridge to transplant; outcomes were improved in the TheraSphere arm compared with the transarterial chemoembolisation arm. The other randomised controlled trial compared TheraSphere plus sorafenib with sorafenib alone as a bridge to transplant; outcomes were similar between treatment groups.

Efficacy and safety of QuiremSpheres

Only one very small case series of QuiremSpheres has been completed in patients with hepatocellular carcinoma. The available data are too limited to draw any conclusions about the safety or efficacy of QuiremSpheres.

Direct comparison of different selective internal radiation therapies

Five small retrospective comparative studies, all rated as being at a high or unclear risk of bias, compared SIR-Spheres with TheraSphere. Two studies included patients who had portal vein thrombosis and appear to have included some of the same patients. Overall survival was reported in four studies, including the

two studies of patients with portal vein thrombosis; overall survival was longer in the TheraSphere arm in three of the studies. One study assessed progression-free survival, which was longer with SIR-Spheres, and another study assessed time to progression, which was longer with TheraSphere (in patients with portal vein thrombosis). The tumour response rate was higher in the TheraSphere arm than in the SIR-Spheres arm in patients with portal vein thrombosis.

Clinical toxicities were generally more frequent with SIR-Spheres than with TheraSphere in one very small study. In a study of patients with portal vein thrombosis, there was no difference in the frequency of fatigue, but pain and nausea appeared to be more frequent with SIR-Spheres, and anorexia appeared to be more frequent with TheraSphere.

No studies that directly compared QuiremSpheres with either SIR-Spheres or TheraSphere were identified. An addendum was received from Terumo Europe NV (Leuven, Belgium) in August 2019 describing a very small pilot study with several methodological limitations.

Network meta-analysis results

The base-case network meta-analysis was in adults with unresectable hepatocellular carcinoma who were categorised as Child–Pugh class A and ineligible for conventional transarterial therapy in the per-protocol population. Three studies were included: two randomised controlled trials comparing SIR-Spheres with sorafenib (SARAH and SIRveNIB) and one randomised controlled trial comparing lenvatinib with sorafenib (REFLECT: Kudo M, Finn RS, Qin S, Han KH, Ikeda K, Piscaglia F, *et al.* Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. *Lancet* 2018;**391**:1163–73). The results provided no evidence that the random-effects model should be preferred. Therefore, the results of the fixed-effects model were used for the base-case and scenario analyses.

There were no meaningful differences in overall survival between any of the three treatments in the per-protocol or intention-to-treat populations. In the per-protocol population, SIR-Spheres showed a non-significant marginal improvement in overall survival when compared with sorafenib (hazard ratio 0.94, 96% credible interval 0.77 to 1.14), although the credible interval indicates that this result is uncertain. SIR-Spheres was ranked as the most efficacious therapy, with a probability of being the best of 0.61. Sorafenib was ranked as the worst treatment, with a probability of being the best of 0.16. Lenvatinib was ranked as the second best, with a probability of being the best of 0.22.

To produce an efficacy estimate for TheraSphere, a sensitivity analysis included the only study that directly compared TheraSphere with SIR-Spheres for Child–Pugh class A patients ineligible for conventional transarterial therapy (Biederman DM, Titano JJ, Tabori NE, Pierobon ES, Alshebeeb K, Schwartz M, *et al.* Outcomes of radioembolization in the treatment of hepatocellular carcinoma with portal vein invasion: resin versus glass microspheres. *J Vasc Interv Radiol* 2016;**27**:812–21.e2). Adding this study had a substantial effect on the network meta-analysis results. In the per-protocol population, TheraSphere showed a significant improvement in overall survival when compared with SIR-Spheres (hazard ratio 0.44, 95% credible interval 0.20 to 0.84), sorafenib (hazard ratio 0.41, 95% credible interval 0.20 to 0.77) and lenvatinib (hazard ratio 0.40, 95% credible interval 0.18 to 0.78). However, these results may be biased and unreliable as the Biederman *et al.* study is a low-quality retrospective study reporting a very strong treatment effect on overall survival for TheraSphere compared with SIR-Spheres (hazard ratio 0.40, 95% credible interval 0.20 to 0.78). A sensitivity analysis excluding the Asia-Pacific SIRveNIB study from the network meta-analysis had very little impact on the results for overall survival in the per-protocol and intention-to-treat populations compared with the base case; there were no significant differences in treatment effects for any comparisons.

Results of economic modelling

The Sirtex and BTG Ltd (hereafter BTG) company submissions each present the methods and results of two separate economic evaluations that split the population potentially eligible for selective internal

radiation therapy into two groups: patients eligible for conventional transarterial therapy and patients ineligible for conventional transarterial therapy. In the corrected version of the BTG conventional transarterial therapy-eligible population, the probabilistic incremental cost-effectiveness ratio for selective internal radiation therapy compared with drug-eluting bead transarterial chemoembolisation was £24,647. In the corrected version of the BTG conventional transarterial therapy-ineligible population, the probabilistic incremental cost-effectiveness ratio for TheraSphere compared with regorafenib (Stivarga®, Bayer plc, Leverkusen, Germany) was £69,070. The economic assessment in the conventional transarterial therapy-eligible population submitted by Sirtex was a cost-minimisation analysis, and found that the costs of selective internal radiation therapy overlapped significantly with those of conventional transarterial therapy. The base-case economic analysis submitted for the conventional transarterial therapy-ineligible population by Sirtex was in a subgroup of patients with low tumour burden and preserved liver function. The results of the presented probabilistic analysis predicted that SIR-Spheres dominated sorafenib (lower costs and higher quality-adjusted life-years).

The results of the Assessment Group's base-case analysis (probabilistic) suggested that TheraSphere is cost-saving relative to both SIR-Spheres and QuiremSpheres. However, incremental costs between TheraSphere and SIR-Spheres were small, and pairwise net monetary benefit was close to zero (–£182). QuiremSpheres was associated with substantial incremental costs of £6615 relative to both TheraSphere and SIR-Spheres (exclusive of Patient Access Scheme). Pairwise net monetary benefit between QuiremSpheres and TheraSphere in the Assessment Group's base case was, therefore, negative, at –£6599. In analyses presented in *Appendix 17*, which include available Patient Access Scheme discounts, QuiremSpheres remained more costly than both TheraSphere and SIR-Spheres; thus, the pairwise net monetary benefit remained negative.

In a fully incremental analysis at list price, none of the three selective internal radiation therapies was predicted to be cost-effective at any willingness-to-pay threshold, being more costly and less effective than lenvatinib. The predicted net monetary benefit for lenvatinib compared with TheraSphere (the lowest-costing selective internal radiation therapy) was –£2154. In a pairwise comparison of sorafenib with TheraSphere, the incremental cost-effectiveness ratio for sorafenib was £31,974 per quality-adjusted life-year gained, with an estimated net monetary benefit of –£150 (implying that TheraSphere is cost-effective compared with sorafenib at a willingness-to-pay threshold of £30,000).

In a fully incremental analysis conducted including confidential Patient Access Scheme discounts, lenvatinib remained the most cost-effective therapy and dominated all selective internal radiation therapies, generating greater health benefits at lower costs. In pairwise comparisons of sorafenib with each selective internal radiation therapy, sorafenib also dominated all selective internal radiation therapies.

A number of scenarios were produced to explore the effect of using data from more restrictive but clinically effective subpopulations, downstaging to potentially curative therapy, different resource use, cost assumptions and data sources. When the modelled population was limited to only those with a low tumour burden and preserved liver function, the incremental cost-effectiveness ratios for TheraSphere and SIR-Spheres were £17,165 and £18,783, respectively, per quality-adjusted life-year gained versus the most cost-effective systemic therapy at list price. The most optimistic incremental cost-effectiveness ratios were produced when downstaging to curative therapy was permitted in this more selective population; incremental cost-effectiveness ratios for TheraSphere and SIR-Spheres decreased to £1440 and £2339, respectively. However, there was no scenario in which selective internal radiation therapy was predicted to be cost-effective at a willingness-to-pay threshold of £30,000 when confidential Patient Access Scheme discounts were included.

Discussion

The Assessment Group's analyses predicted lenvatinib to be the most cost-effective treatment in nearly all scenarios, and sorafenib was generally the most cost-effective alternative, producing more quality-adjusted life-years at a higher cost. The results of the Assessment Group's base-case analysis are robust to changes in a wide range of assumptions and across different scenarios.

Strengths of the Assessment Group model include:

- High-quality randomised controlled trial data were included to model the outcomes of the patient population most relevant to UK practice.
- Analyses included all appropriate comparators.
- There was independent modelling of the costs and outcomes of patients who receive work-up but were ineligible to receive selective internal radiation therapy.
- There was preserved randomisation and internal consistency with regard to the use of subsequent systemic and curative therapies.

Insurmountable limitations in the evidence base meant that the Assessment Group was unable to address the question of selective internal radiation therapy's cost-effectiveness in patients with early- and intermediate-stage hepatocellular carcinoma. The evidence for the use of TheraSphere and QuiremSpheres in advanced hepatocellular carcinoma patients was extremely limited, and a lack of head-to-head evidence prevented a meaningful comparison of SIR-Spheres, TheraSphere and QuiremSpheres with one another. This essentially limits this particular comparison to that of a cost minimisation, although a full comparison of the cost-effectiveness of selective internal radiation therapy versus sorafenib and lenvatinib was possible.

Conclusions

Implications for service provision

The existing evidence cannot provide decision-makers with clear guidance on the comparative effectiveness of treatments in early- and intermediate-stage hepatocellular carcinoma.

In the advanced-stage hepatocellular carcinoma population, two large randomised trials have assessed the comparative effectiveness of SIR-Spheres with sorafenib, showing that selective internal radiation therapy has effectiveness similar to that of sorafenib.

None of the selective internal radiation therapies is cost-effective at any willingness-to-pay threshold, being more costly and less effective than lenvatinib; this is the case both at list price and using Patient Access Schemes.

Suggested research priorities

No strong conclusions can be drawn in the early- and intermediate-stage hepatocellular carcinoma populations owing to considerable uncertainty in estimates of effectiveness and high risk of bias. A priority for further research is, therefore, the conduct of studies in these populations.

The low tumour burden/albumin–bilirubin 1 subgroup potentially represents a group of patients for whom selective internal radiation therapy may be beneficial when compared with sorafenib. Future work considering this subgroup may, therefore, be useful.

There is currently very limited evidence on the comparative effectiveness of alternative selective internal radiation therapies. Future high-quality studies evaluating alternative selective internal radiation therapies would be beneficial.

Study registration

This study is registered as PROSPERO CRD42019128383.

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Chapter 1 Background

This report contains reference to confidential information provided as part of the NICE appraisal process. This information has been removed from the report and the results, discussions and conclusions of the report do not include the confidential information. These sections are clearly marked in the report.

Description of health problem

Liver cancer is the fifth most common cancer and the second most frequent cause of cancer-related death globally.[1] Hepatocellular carcinoma (HCC) is the most common type of liver cancer, representing around 90% of primary liver cancers.[1] Around 90% of HCCs are associated with a known underlying aetiology, most frequently chronic viral hepatitis B or C, or overconsumption of alcohol (alcoholic liver disease). Long periods of chronic liver disease, characterised by hepatic inflammation, fibrosis and aberrant hepatocyte regeneration, can cause scarring of the liver (cirrhosis).[2] One-third of patients with cirrhosis will develop HCC during their lifetime.[1]

In the UK, the underlying aetiology of HCC is commonly alcoholic liver disease and non-alcoholic fatty liver disease, with 50% of cases attributable to these factors. Hepatitis infection (hepatitis B or C) is also a common cause in the UK but, in contrast with non-Western populations, represents only 15% of cases. Viral hepatitis is the primary cause of HCC in non-Western populations, with up to 90% of cases directly attributable to the hepatitis B and C virus.[3]

Underlying liver cirrhosis and the burden of a growing tumour results in an often substantially reduced liver function in HCC patients, with consequences for morbidity and mortality. Liver dysfunction associated with chronic liver disease is commonly assessed using the Child–Pugh scoring system, which classifies patients into three groups: A, B or C (least severe disease, moderate liver disease and severe/end-stage liver disease). Treatment options available to HCC patients are in part dictated by liver function, with choices becoming more limited with increasing liver dysfunction. The Barcelona Clinic Liver Cancer (BCLC) staging system is used to establish prognosis and enable the selection of appropriate treatment based on both the underlying liver dysfunction and the cancer stage.[1] A modified version of the BCLC staging system is presented in *Table 1*. The BCLC staging system classifies patients into five stages (0, A, B, C and D) according to tumour burden, liver function and Eastern Cooperative Oncology Group (ECOG) performance status,[4] which must all be considered when selecting appropriate treatment.[1]

Epidemiology

The incidence of HCC is higher in men than in women, with 2128 men and 586 women diagnosed with HCC in England in 2017.[5] The majority of cases occur in adults aged > 60 years.[5] The average age of patients at HCC diagnosis is 66 years, reflecting the long-term nature of most chronic liver disease underlying HCC.[6] Approximately 30% of European patients are diagnosed with early-stage (BCLC stage 0 or A) HCC, approximately 10% are diagnosed with intermediate-stage (BCLC stage B) HCC, approximately 50% are diagnosed with advanced-stage (BCLC stage C) HCC and approximately 10% are diagnosed with terminal (BCLC stage D) HCC.[7] The majority of patients are, therefore, diagnosed with advanced disease, for which treatment options are more limited (see *Current service provision*).

Prognosis

Prognosis of patients with HCC is heavily dependent on the stage of disease, and is summarised in *Table 1*. In very early-stage and early-stage disease, a range of potentially curative treatment options are typically available and, thus, the long-term prognosis of these patients can be good. In very early-stage disease, 5-year survival is between 70% and 90%, and it is between 50% and 70% in early-stage disease.[8] In intermediate- and advanced-stage disease, treatment options are more limited and are

TABLE 1 Modified BCLC staging system and treatment strategy

Prognostic stage	Tumour burden	Liver function	Performance status	Recommended treatment	Survival
Very early stage (BCLC 0)	Single < 2-cm nodule	Preserved liver function	0	Ablation or resection	> 5 years
Early stage (BCLC A)	1–3 nodules of < 3 cm in size	Preserved liver function	0	Ablation, resection or transplant	> 5 years
Intermediate stage (BCLC B)	Multinodular, unresectable	Preserved liver function	0–1	Conventional transarterial therapies (TAE, TACE and DEB-TACE)	> 2.5 years
Advanced stage (BCLC C)	PVI/extrahepatic spread	Preserved liver function	0–2	Systemic therapy [sorafenib,[a] lenvatinib[b] or regorafenib[c] (for patients who have previously had sorafenib)]	≥ 10 months
Terminal stage (BCLC D)	Non-transplantable HCC	End-stage liver function	3–4	Best supportive care	3 months

DEB-TACE, drug-eluting bead transarterial chemoembolisation; PVI, portal vein invasion; TACE, transarterial chemoembolisation; TAE, transarterial embolisation.
a Nexavar®; Bayer plc, Leverkusen, Germany.
b Kisplyx®; Eisai Ltd, Tokyo, Japan.
c Stivarga®; Bayer plc, Leverkusen, Germany.

primarily delivered to prolong survival and reduce the burden of symptoms. Length of survival is, therefore, significantly shorter; prognosis in patients with advanced disease is particularly poor, with a median survival of < 12 months.[8]

Current service provision

Clinical management of HCC is complex. There are a range of treatment options available, which depend on the location and stage of the cancer and liver function. Clinical practice guidelines published by the European Association for the Study of the Liver (EASL) summarise treatment recommendations according to BCLC classification.[1] These recommendations are presented in *Table 1*, with some modifications, reflecting entry criteria to pivotal clinical trials.

The primary aim of therapy in patients diagnosed with early-stage HCC is typically curative, and there are a number of available treatment options with curative potential. These include radiofrequency ablation (which uses the heat generated by alternating currents to destroy solid tumour tissue), resection (in which the tumour-containing portions of the liver are removed) and liver transplantation.[1] Owing to the limited availability of suitable donors, liver transplant is typically reserved for patients with a poor prognosis owing to impaired liver function, and in whom resection is inappropriate, for example in patients with multifocal tumours. Suitability for transplant is assessed against the Milan criteria,[9] which require patients to have a single lesion of < 5 cm, or up to three lesions of < 3 cm each, without macroscopic vascular invasion (MVI).[1] Typically, patients not meeting these criteria are ineligible for a transplant, but increasingly patients whose disease has been 'downstaged' may be considered for transplant. Downstaging is when patients whose tumours fall outside the limits permitted by the Milan criteria[9] are brought within the criteria, typically through the use of conventional transarterial therapies (CTTs) (see below) to reduce tumour burden. Patients waiting for a transplant may also receive CTT as a 'bridging therapy', in which the intent is to control the progression of disease to keep patients within the Milan criteria.[9] However, as transplant waiting times in the UK are typically relatively short, with a median time for HCC patients of approximately 50 days, the use of bridging therapy is limited.

Conventional transarterial therapies are the standard care in intermediate HCC if resection or other curative treatment modalities are unsuitable. CTT includes transarterial chemoembolisation (TACE), drug-eluting bead transarterial chemoembolisation (DEB-TACE) and transarterial embolisation (TAE) without chemotherapy. Blood is primarily supplied to the liver via the hepatic portal vein, whereas most tumours are supplied by the hepatic artery. All three forms of CTT work by administering an embolising agent into the hepatic artery to block blood vessels feeding the tumours within the liver. This process preferentially interrupts the blood supply to the tumours, while allowing blood to continue to reach the remaining healthy tissue. In the case of TACE, Lipiodol® (Guerbet, Villepinte, France) is combined with a chemotherapy agent, typically doxorubicin or cisplatin, which is administered directly to the tumour, allowing for much higher concentrations of the drug to be achieved than could be tolerated systemically. In DEB-TACE, drug-eluting beads typically bound with doxorubicin or epirubicin are administered to the tumour via the hepatic artery. This allows the release of the chemotherapeutic agent over a prolonged period of time, thereby reducing systemic concentrations (and thus any side effects) compared with TACE.[10] TAE, or bland TACE, involves only the physical occlusion of blood vessels, with no addition of chemotherapy. Because the primary therapeutic effect of CTT is the embolisation of the hepatic artery, the use of these techniques is typically limited to patients with good portal vein flow, so as to maintain a good blood supply to the liver. Therefore, patients with portal vein thrombosis (PVT) or tumour invasion of the portal vein are typically considered contraindicated to CTT.

In patients who have advanced HCC, or for whom CTT has previously failed, the current standard of care consists of systemic chemotherapy. Current National Institute for Health and Care Excellence (NICE) guidance in this population recommends sorafenib (Nexavar®; Bayer plc, Leverkusen, Germany) as an option for people with Child–Pugh class A liver impairment (TA474).[11] Lenvatinib (Kisplyx®, Eisai Ltd, Tokyo, Japan) is also recommended as an option for people with Child–Pugh class A liver impairment and an ECOG performance status of 0 or 1 (TA551).[12] A recent technology appraisal on regorafenib (Stivarga®; Bayer plc, Leverkusen, Germany) for treating advanced unresectable HCC (TA555)[13] recommends regorafenib as an option for people who have previously been treated with sorafenib and have Child–Pugh class A liver impairment and an ECOG performance status of 0 or 1. Best supportive care (BSC) is offered to patients when CTTs or systemic therapy are not available or appropriate, including patients with terminal-stage disease.

Description of the technology under assessment

Selective internal radiation therapy (SIRT), also known as transarterial radioembolisation (TARE), is a complex intervention that delivers radiation directly to liver tumours via microspheres that are injected into the hepatic artery via a catheter inserted into the femoral artery. The most likely position for SIRT in the HCC treatment pathway is for patients with intermediate-stage (BCLC stage B) or advanced-stage (BCLC stage C) HCC as a non-curative option, as the use of SIRT is not precluded by reduced liver function as strictly as CTTs. However, SIRT is unlikely to be suitable for patients with more limited liver function (Child–Pugh class $\geq$ B8) or extrahepatic tumour spread. There may also be a role for SIRT as a bridging therapy for BCLC stage A patients awaiting transplant (see *Current service provision*) as an alternative to CTTs.

The NICE interventional procedures guidance 460[14] states that current evidence on the efficacy and safety of SIRT for primary HCC was adequate to permit routine use of the technology. However, significant uncertainties remain about its comparative effectiveness relative to conventional transarterial and systemic therapeutic options.[14] Clinicians have been encouraged by NICE to enter eligible patients into trials comparing the procedure against other forms of treatment and to enrol all patients into the UK SIRT registry (launched in 2013).[14]

The present appraisal concerns three SIRTs: SIR-Spheres® (Sirtex Medical Ltd, Woburn, MA, USA), TheraSphere™ [BTG Ltd, London, UK (now Boston Scientific, Marlborough, MA, USA)] and QuiremSpheres® (Quirem Medical BV, Deventer, the Netherlands). SIR-Spheres [manufactured by Sirtex Medical Ltd (hereafter Sirtex)] is a Conformité Européenne (CE)-marked class III active medical device comprising resin microspheres containing yttrium-90; SIR-Spheres is indicated for the treatment of inoperable liver tumours. TheraSphere [manufactured by BTG Ltd (hereafter BTG)] is a CE-marked class III active medical device comprising glass microspheres containing yttrium-90; TheraSphere is indicated for the treatment of hepatic neoplasia. QuiremSpheres [manufactured by Quirem Medical BV and distributed by Terumo Europe NV (Leuven, Belgium)] is a CE-marked class III active medical device comprising poly-L-lactic acid (PLLA) microspheres containing holmium-166; QuiremSpheres is indicated for the treatment of unresectable liver tumours.

In preparation for SIRT, patients undergo preliminary angiography of the hepatic artery, and protective coiling of extrahepatic branches to reduce extrahepatic radiation uptake. For TheraSphere and SIR-Spheres, technetium-99m-macroaggregated albumin is used as an imaging surrogate and injected into the hepatic artery using the same catheter position chosen for the scheduled SIRT session. Calculation of the radiation dose to the tumour and adjacent liver, hepatopulmonary shunt fraction and tracer distribution are evaluated with single-photon emission computerised tomography (SPECT) imaging. This is known as the 'work-up' procedure, and is ultimately what decides whether or not patients are eligible to receive SIRT. A high level of lung shunt or extrahepatic uptake contraindicate the SIRT procedure. When SIRT is not contraindicated following work-up, patients are later readmitted for the SIRT procedure, which is performed in a lobar, sectorial or segmental approach according to tumour size and location.[1] When tumours are present in both lobes, patients may receive a separate administration of SIRT to each lobe on separate occasions (often several weeks apart), to allow clinicians to monitor the liver's response to radiation and prevent damage.

The work-up procedure for QuiremSpheres exploits the properties of holmium-166 microspheres, which, unlike yttrium-90, can be visualised with SPECT and magnetic resonance imaging (MRI) even at low concentrations. Therefore, a lower dose of holmium-166 is used for evaluating dose distribution [known as QuiremScout® (Quirem Medical BV)], rather than a surrogate, which may allow for a more accurate assessment of radiation distribution and dosimetry.

Table 2 presents an overview of the main characteristics of each therapy.

TABLE 2 Main characteristics of SIR-Spheres, TheraSphere and QuiremSpheres

Technique	SIR-Spheres	TheraSphere	QuiremSpheres
Radioactive isotope	Yttrium-90	Yttrium-90	Holmium-166
Microsphere material	Resin	Glass	PLLA
Therapeutic mode of action	Beta radiation	Beta radiation	Beta radiation
Mean diameter of the microsphere (μm)	32.5	20–30	30
Half-life of the radioactive isotope (hours)	64.1	64.1	26.8
Specific activity per microsphere (Bq)	50	2500	350
Typical administered activity (GBq)	1.4–2.0	–	–
Typical number of microspheres administered (millions)	30–40	4	20–30
Time for 90% of dose to be deposited (days)	11	11	4

Chapter 2 Definition of the decision problem

The decision problem in terms of participants, interventions, comparisons, outcomes, study design and other key issues

The decision problem relates to the use of the three SIRTs, TheraSphere, SIR-Spheres and QuiremSpheres, within their approved indications for the treatment of HCC. Relevant comparators are each other, CTTs (i.e. TAE, TACE and DEB-TACE) or, for people for whom any transarterial therapies are inappropriate, established clinical management without SIRT, such as systemic therapy (sorafenib, lenvatinib or regorafenib) or BSC.

Overall aims and objectives of the assessment

This appraisal will assess the clinical effectiveness and cost-effectiveness of the SIRT (TheraSphere, SIR-Spheres and QuiremSpheres) for treating HCC.

The objectives of the assessment are to evaluate the:

- clinical effectiveness of each intervention
- adverse effect profile of each intervention
- incremental cost-effectiveness of each intervention compared with (1) each other, (2) CTTs, (3) systemic therapy and (4) BSC.

Chapter 3 Assessment of clinical effectiveness

Methods for reviewing clinical effectiveness

A systematic review of the clinical effectiveness evidence on SIRT was undertaken following the general principles outlined in the Centre for Reviews and Dissemination (CRD)'s guidance on undertaking systematic reviews[15] and reported in accordance with the general principles of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[16] The research protocol is registered on PROSPERO, the international prospective register of systematic reviews in health and social care (registration number CRD42019128383).

Search strategy

A comprehensive search was undertaken to systematically identify clinical effectiveness and cost-effectiveness literature relating to TheraSphere, SIR-Spheres and QuiremSpheres for HCC. In addition, a search for randomised controlled trials (RCTs) of comparator therapies was undertaken to strengthen the network of evidence on SIRT.

Search strategy for selective internal radiation therapy studies

A search strategy was developed in Ovid MEDLINE by an information specialist (MH), with input from the review team. The strategy consisted of a set of terms for HCC combined with terms for SIRT, and was limited to studies from 2000 onwards. The 2000 date limit was applied as scoping searches had identified controlled studies of SIR-Spheres and TheraSphere published after the year 2000; earlier studies were preliminary uncontrolled studies so have limited value for addressing the decision problem. In addition, clinical advice confirmed that the treatment environment for patients with HCC was different prior to 2000 in terms of comparator treatment options. The searches were not limited by language or study design. The MEDLINE strategy was adapted for use in all other resources searched.

The following databases were searched on 28 January 2019:

- MEDLINE (all) (via Ovid)
- EMBASE (via Ovid)
- Cumulative Index to Nursing and Allied Health Literature (CINAHL) Plus
- Science Citation Index (via Web of Science)
- Cochrane Central Register of Controlled Trials (CENTRAL) (via Wiley)
- Cochrane Database of Systematic Reviews (via Wiley)
- Database of Abstracts of Reviews of Effects (via CRD databases)
- Health Technology Assessment (HTA) database (via CRD databases)
- NHS Economic Evaluation Database (NHS EED) (via CRD databases)
- EconLit (via Ovid).

In addition, information on studies in progress, unpublished research or research reported in grey literature was sought by searching a range of relevant resources:

- ClinicalTrials.gov
- World Health Organization (WHO) International Clinical Trials Registry portal
- European Union Clinical Trials Register
- PROSPERO
- Conference Proceedings Citation Index – Science (via Web of Science)
- ProQuest Dissertations & Theses A&I (via ProQuest).

A search of the NICE website and NHS Evidence for relevant guidelines was undertaken on 8 May 2019.

Company submissions and relevant systematic reviews were also hand-searched to identify further relevant studies. Clinical advisors were consulted for any additional studies.

Search results were imported into EndNote X9 (Clarivate Analytics, Philadelphia, PA, USA) and de-duplicated. Full search strategies can be found in *Appendix 1*.

Search strategy for comparator therapies

A search for RCTs of comparator therapies was undertaken to strengthen the network of evidence on SIRT. In view of time and resource limitations, it was decided to identify RCTs of CTTs (i.e. TAE, TACE and DEB-TACE) by searching existing relevant systematic reviews and meta-analyses and undertaking update searches if necessary.

Evidence on systemic therapies for HCC was identified from the recent NICE single technology appraisals of sorafenib,[11] lenvatinib[12] and regorafenib.[13]

The search strategy for systematic reviews and meta-analyses of CTTs was developed in Ovid MEDLINE by an information specialist (MH), with input from the review team. The strategy consisted of a set of terms for HCC combined with terms for embolisation or chemoembolisation, and was limited to studies from 2010 onwards to identify the most recent reviews. A search strategy to limit retrieval to systematic reviews or meta-analyses was added in MEDLINE and EMBASE.[17] The MEDLINE strategy was adapted for use in all resources searched.

The following databases were searched on 7 May 2019:

- MEDLINE (all) (via Ovid)
- EMBASE (via Ovid)
- Cochrane Database of Systematic Reviews (via Wiley)
- Database of Abstracts of Reviews of Effects (via CRD databases)
- HTA database (via CRD databases).

In addition, PROSPERO was searched to identify any unpublished or ongoing systematic reviews or meta-analyses.

Search results were imported into EndNote X9 and de-duplicated. Full search strategies can be found in *Appendix 2*.

Inclusion criteria

Inclusion criteria were defined in line with the final scope provided by NICE and are outlined below. Studies were initially assessed for relevance using titles and abstracts. One reviewer examined titles and abstracts, with a second reviewer checking 10% of records. Full manuscripts of any titles/abstracts that appeared to be relevant were obtained if possible and the relevance of each study was assessed independently by two reviewers in accordance with the criteria outlined in the following sections. Any discrepancies were resolved through consensus and, if necessary, a third reviewer was consulted. Relevant foreign-language studies were translated and assessed for inclusion in the review. Studies available only as abstracts were included and attempts were made to contact authors for further data.

Study design

Randomised controlled trials were eligible for inclusion in the clinical effectiveness review. However, where RCT evidence was insufficient to address the decision problem, non-randomised comparative studies (including retrospective studies) and non-comparative studies of SIRT were considered for

inclusion. The evidence was scoped before deciding what level of evidence would be included for data extraction and quality assessment.

Participants

Studies of people with early-stage HCC in whom curative treatment is contraindicated (BCLC stage A), and with intermediate-stage (BCLC stage B) or advanced-stage (BCLC stage C) HCC, with or without PVT/portal vein invasion (PVI), were included in the review. Studies of people with secondary liver metastases or other types of liver cancer (such as cholangiocarcinoma) were not included unless they also included people with primary HCC, and results were reported separately for people with HCC.

Interventions

The interventions under consideration were the selective internal radiation therapies TheraSphere, SIR-Spheres and QuiremSpheres. Studies in which more than one type of SIRT was used were included only if results were reported separately for the different types of SIRT. Where studies did not state which type of SIRT or radioembolisation technology was used, authors were contacted to identify the specific technology used.

Evidence on combined treatments (e.g. SIRT plus sorafenib) was also considered for inclusion, and evidence was scoped before deciding which trials would be included for data extraction and quality assessment.

Comparators

Relevant comparators were:

- alternative SIRT interventions (i.e. TheraSphere, SIR-Spheres and QuiremSpheres)
- conventional transarterial therapies (i.e. TAE, TACE and DEB-TACE)
- established clinical management without SIRT, such as systemic therapy (i.e. sorafenib, lenvatinib and regorafenib) or BSC, for people for whom any TAE therapies are inappropriate.

To strengthen the network of evidence on SIRT, we considered undertaking comparisons of CTTs (i.e. TAE, TACE and DEB-TACE), systemic therapies (i.e. sorafenib, lenvatinib and regorafenib) and BSC, using RCT evidence. The evidence was scoped and criteria for inclusion were developed. Relevant RCTs were assessed for quality and key outcome data were extracted, based on requirements for the model.

Outcomes

The outcome measures to be considered included:

- overall survival (OS)
- progression-free survival (PFS)
- time to progression (TTP)
- response rates
- rates of liver transplant or surgical resection
- adverse effects of treatment
- health-related quality of life (HRQoL)
- time on treatment/number of treatments provided.

Data extraction

Data were extracted by one reviewer using a standardised data extraction form and independently checked for accuracy by a second reviewer. Disagreements were resolved through consensus and, if necessary, a third reviewer was consulted. If multiple publications of the same study were identified, data were extracted and reported as a single study.

Critical appraisal

The methodological quality of the included studies was assessed using criteria relevant to the study design. RCTs were assessed using the most recent version of the Cochrane risk-of-bias tool.[18] Quality-assessment tools for other study designs were developed using relevant criteria, such as those outlined in the CRD's guidance on undertaking systematic reviews.[15] Quality assessment was undertaken by one reviewer and independently checked by a second reviewer. Any disagreements were resolved through consensus and, if necessary, a third reviewer was consulted. Details of the quality of the included studies are presented in descriptive tables and their impact on the reliability of results is discussed.

Methods of data analysis/synthesis

Characteristics of the included SIRT studies (such as participant and intervention characteristics, results and trial quality) were tabulated and described in a narrative synthesis. Where sufficient clinically and statistically homogenous data were available, data were pooled using appropriate meta-analytic techniques using WinBUGS software (Medical Research Council Biostatistics Unit, Cambridge, UK). Clinical, methodological and statistical heterogeneity were investigated, with sensitivity or subgroup analyses undertaken where appropriate and where available data permitted.

Where the data allowed, a network meta-analysis (NMA) using Bayesian statistical methods with WinBUGS software was undertaken to estimate the relative effectiveness of the different treatments. Results are summarised using point estimates and 95% credible intervals (CrIs) of the effect of each treatment relative to the reference treatment. Where possible, consistency between direct and indirect estimates of treatment effect in the NMA was assessed. The results of the NMA are described in *Chapter 4* of this report and were used in the economic model described in *Chapter 7*.

Clinical effectiveness results

Quantity and quality of research available

Studies of selective internal radiation therapy

The electronic searches for clinical effectiveness evidence on SIRT interventions (i.e. TheraSphere, SIR-Spheres and QuiremSpheres) identified a total of 4755 records (after de-duplication between databases). The 4755 records were inserted into an EndNote library. Reviewer 1 (RW) screened 2615 titles and abstracts, and reviewer 2 (SS) screened 2617 titles and abstracts. A total of 477 records (10% of the library) were double-screened; discrepancies were resolved through consensus or in consultation with a third reviewer (AE).

Of the 4755 records in the library, 3670 were excluded from the clinical effectiveness review after title and abstract screening as they did not include patients with unresectable HCC, did not assess TheraSphere, SIR-Spheres or QuiremSpheres, did not report relevant patient outcomes or were not a primary study. A total of 1085 records appeared to meet the study selection criteria based on title and abstract (where an abstract was available).

In view of the large number of potentially eligible records, the evidence was scoped before deciding which studies to order for full-paper screening. Records were coded, using titles and abstracts (where available), in terms of the intervention (type of SIRT and whether the study focused on the delivery of SIRT or the work-up procedure), the study design (prospective or retrospective, comparative or not) and the number of HCC patients included in the study. A large number of records were conference/meeting abstracts ($n = 603$) rather than full publications ($n = 482$); reviewer 1 (RW) coded the full publications and reviewer 2 (SS) coded the conference/meeting abstracts. Studies marked as a 'RCT' ($n = 47$; 43 full publications and four conference/meeting abstracts) or as 'prospective comparative' ($n = 26$;

18 full publications and eight conference/meeting abstracts) or 'retrospective comparative' ($n = 103$; 61 full publications and 42 conference/meeting abstracts) studies were ordered for full-paper screening as comparative studies (total $n = 176$) were prioritised over non-comparative studies. However, it was clear that there were no comparative studies of QuiremSpheres; therefore, all studies considered to relate to QuiremSpheres (referring to holmium as the intervention) were ordered for full-paper screening ($n = 11$). In addition, large non-comparative studies that included > 500 patients were also ordered for full-paper screening ($n = 6$). One additional non-comparative study, in which BCLC subgroups and subsequent treatments were reported and which was considered to be particularly relevant for the economic model, was ordered. Therefore, a total of 194 records were ordered for full-paper screening.

Of the 194 records ordered, 130 were excluded based on full-paper screening and 64 were considered to be potentially relevant records to be included in the clinical effectiveness review and/or NMA (55 studies plus nine associated publications).

A total of 130 records were coded at the title and abstract stage as systematic reviews. Reviewer 1 (RW) screened systematic reviews from 2015 onwards for relevance; there were 25 relevant systematic reviews (plus one associated erratum). The reference lists of these systematic reviews were screened to check for additional potentially relevant studies; no additional studies were identified.

Separate searches of guideline databases (the NICE website and NHS Evidence), conducted in May 2019, identified a total of 23 records after de-duplication against the original library, none of which were considered relevant for inclusion in the systematic review. The reference lists of relevant guidelines were screened to check for additional potentially relevant studies; no additional studies were identified.

Clinical advisors were not aware of any additional studies other than those already identified from electronic searches.

A PRISMA flow diagram is presented in *Figure 1*. In total, 27 of the 55 studies were prioritised for data extraction, as they were considered to be the most relevant for the assessment of clinical effectiveness and/or the proposed NMAs; these studies are summarised in *Table 3*. One non-comparative study was included in the clinical effectiveness review because this was the only study of QuiremSpheres;[51] the other 26 studies were comparative studies.

The 28 lower-priority studies are summarised in *Appendix 7* along with the reason for not including them in the systematic review of clinical effectiveness or the proposed NMAs (e.g. consultation with clinical advisors confirmed that the comparators used were not applicable to current UK practice).[52–55]

Thirty-four records were coded at the title and abstract stage as potentially relevant economic studies (seven of which were also coded as includes for the clinical effectiveness review). A separate flow diagram of the study selection process for these economic studies is presented (see *Figure 7*).

Studies of comparator therapies

Randomised controlled trials of comparator therapies were sought to strengthen the network of evidence on SIRT (see *Chapter 5*). The search for systematic reviews and meta-analyses of CTTs (TAE, TACE and DEB-TACE) identified 989 records. The records were inserted into an EndNote library and one reviewer (RW) screened the titles and abstracts. Records were put in reverse date order and screened started at the year 2019 and worked backwards until no new relevant RCTs were identified from the reviews and meta-analyses. A total of 319 records were screened, published between 2017 and 2019. Twenty-four of the 319 records were relevant systematic reviews or meta-analyses; full papers were obtained and reference lists were checked for RCTs comparing TAE, TACE or DEB-TACE

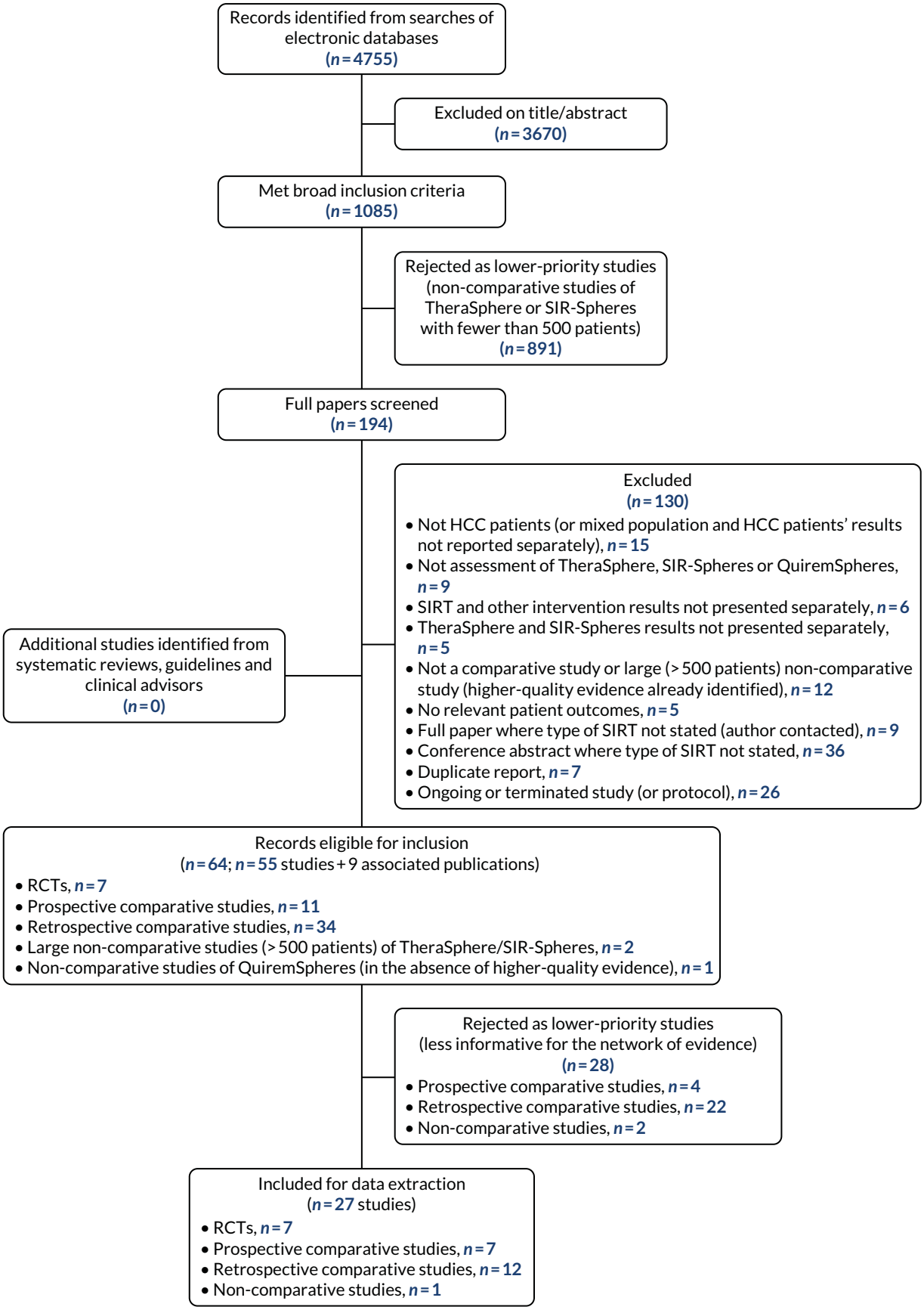

FIGURE 1 The PRISMA flow diagram of the study selection process for the clinical effectiveness review.

TABLE 3 Studies included in the systematic review of clinical effectiveness or considered for the NMA ($n = 27$)

Study (first author and year)	Intervention	Comparator	Location	Population
***RCTs of SIR-Spheres* (n = *5*)**				
Vilgrain 2017[19] and Bouattour 2017[20] SARAH	SIR-Spheres	Sorafenib	France	Adults with locally advanced HCC (BCLC C) or new HCC not eligible for surgical resection, transplant or thermal ablation after a previously cured HCC (cured by surgery or thermoablative therapy) or HCC with two unsuccessful rounds of TACE
Chow 2018[21] SIRveNIB	SIR-Spheres	Sorafenib	Asia-Pacific region	Adults with locally advanced HCC (BCLC B or C) not amenable to curative treatment
Kolligs 2015[22] SIRTACE	SIR-Spheres	TACE	Germany and Spain	Adults with unresectable liver-only HCC (without portal vein occlusion)
Pitton 2015[23]	SIR-Spheres	DEB-TACE	Germany	Adults with unresectable N0, M0 HCC (BCLC stage B)
Ricke 2015[24] SORAMIC	SIR-Spheres plus sorafenib	Sorafenib alone	Germany	Adults with unresectable intermediate or advanced HCC (BCLC stage B or C), with preserved liver function (Child–Pugh class $\leq$ B7) and ECOG < 2, who were poor candidates for TACE (including those failing TACE)
***RCTs of TheraSphere* (n = *2*)**				
Salem 2016,[25] Gabr 2017[26] and Gordon 2016[27] PREMIERE	TheraSphere	TACE	USA	Adults with BCLC stage A/B unablatable/ unresectable HCC with no vascular invasion, Child–Pugh class A/B
Kulik 2014,[28] Lewandowski 2016[29] and Vouche 2013[30]	TheraSphere	TheraSphere plus sorafenib	USA	Adults with Child–Pugh class $\leq$ B8 and potential candidates for orthotopic liver transplant
***Prospective comparative studies of TheraSphere* (n = *7*)**				
Kirchner 2019[31]	TheraSphere	TACE/DEB-TACE	Germany	Adults with unresectable HCC
El Fouly 2015[32]	TheraSphere	TACE	Germany and Egypt	Adults with intermediate-stage (BCLC B) unresectable HCC and good liver function (Child–Pugh class < B7)
Salem 2013[33]	TheraSphere	TACE	USA	Adults with treatment-naive HCC with ECOG 0–2
Memon 2013[34]	TheraSphere	TACE	USA	Adults with HCC that progressed after intra-arterial locoregional therapies (TACE and SIRT)
Hickey 2016[35]	TheraSphere	TACE	USA	Adults with unresectable HCC and bilirubin $\leq$ 3.0 mg/dl
Maccauro 2014[36]	TheraSphere plus sorafenib	TheraSphere alone	Italy	Adults with unresectable HCC (Child–Pugh class A)
Woodall 2009[37]	TheraSphere	BSC	USA	Adults with unresectable HCC (including both patients with and patients without PVT)

continued

TABLE 3 Studies included in the systematic review of clinical effectiveness or considered for the NMA ($n = 27$) (*continued*)

Study (first author and year)	Intervention	Comparator	Location	Population
***Retrospective comparative studies of SIR-Spheres vs. TheraSphere* (n = 5)**				
Biederman 2015[38]	SIR-Spheres	TheraSphere	USA	Adults with HCC with PVT
Biederman 2016[39]	SIR-Spheres	TheraSphere	USA	Adults with HCC with PVI
Van Der Gucht 2017[40]	SIR-Spheres	TheraSphere	Switzerland	Adults with unresectable HCC
Bhangoo 2015[41]	TheraSphere	SIR-Spheres	USA	Adults with unresectable HCC
d'Abadie 2018[42]	SIR-Spheres	TheraSphere	Belgium	Adults with HCC
***Retrospective comparative studies of SIR-Spheres* (n = 4)**				
Cho 2016[43]	SIR-Spheres	Sorafenib	Korea	Adults with BCLC stage C HCC with PVT
de la Torre 2016[44]	SIR-Spheres	Sorafenib	Spain	Adults with HCC with PVI
Gramenzi 2015[45]	SIR-Spheres	Sorafenib	Italy	Adults with HCC unfit for other effective therapies, Child–Pugh class A/B, performance status ≤ 1, no metastases and no previous systemic chemotherapy
Soydal 2016[46]	TACE	SIR-Spheres	Turkey	Adults with BCLC B or C HCC
***Retrospective comparative studies of TheraSphere* (n = 3)**				
Salem 2011[47]	TheraSphere	TACE	USA	Adults with unresectable HCC and bilirubin 3.0 mg/dl
Moreno-Luna 2013[48]	TheraSphere	TACE	USA	Adults with unresectable HCC
Akinwande 2016[49,50]	TheraSphere	DEB-TACE	USA	Adults with unresectable HCC (with or without PVT)
***Non-comparative studies of QuiremSpheres* (n = 1)**				
Radosa 2019[51]	QuiremSpheres	N/A	Germany	Adults with HCC

N/A, not applicable; PREMIERE, Prospective Randomized study of chEmoeMbolization versus radIoEmbolization for the tReatment of hEpatocellular carcinoma; SARAH, SorAfenib versus Radioembolization in Advanced Hepatocellular Carcinoma; SIRveNIB, Selective Internal Radiation Therapy Versus Sorafenib in Locally Advanced Hepatocellular Carcinoma.

with each other. Eleven relevant RCTs (reported in 12 publications) were identified, which are summarised in *Table 4*. In view of the recency of the relevant systematic reviews and meta-analyses and the age of the RCTs of CTTs (published between 1992 and 2016), it was decided that update searches were not necessary.

Evidence on systemic therapies for HCC was identified from the recent NICE single technology appraisals of sorafenib,[11] lenvatinib[12] and regorafenib.[13]

Assessment of clinical effectiveness

This section describes the seven RCTs and seven prospective comparative studies of SIR-Spheres and TheraSphere, the five retrospective comparative studies comparing SIR-Spheres with TheraSphere and the non-comparative case series of QuiremSpheres. The additional seven retrospective comparative studies of SIR-Spheres or TheraSphere (see *Table 3*) and studies of comparator therapies (see *Table 4*) that were selected, as they were considered to be potentially relevant for the NMAs, are described in *Chapter 5*.

TABLE 4 The RCTs of CTTs ($n = 11$)

Study (first author and year)	Intervention	Comparator	Population
Lammer 2010[56] and Vogl 2011[57] PRECISION V	DEB-TACE	TACE	Adults with HCC unsuitable for resection or percutaneous ablation (BCLC A/B without portal invasion or extrahepatic spread)
Golfieri 2014[58]	DEB-TACE	TACE	Adults with HCC unsuitable for curative treatment or had failed/recurred after resection/ablation
Sacco 2011[59]	DEB-TACE	TACE	Adults with previously untreated unresectable HCC not suitable for ablative treatment, Child–Pugh class A or B and ECOG score of 0/1, absence of PVT and extrahepatic metastases
van Malenstein 2011[60]	DEB-TACE	TACE	Adults with HCC who were not candidates for curative treatments, Child–Pugh class A or B cirrhosis and an ECOG score of 0 or ECOG score of < 3 if the restriction in status was not because of the HCC
Llovet 2002[61]	TACE	TAE	White patients with unresectable HCC not suitable for curative treatment, or Child–Pugh class A or B and Okuda stage I or II
Kawai 1992[62]	TACE	TAE	HCC patients
Chang 1994[63]	TACE	TAE	Untreated patients with inoperable HCC
Meyer 2013[64]	TACE	TAE	Patients aged ≥ 16 years with HCC not eligible for surgical resection
Yu 2014[65]	TACE	TAE	Unresectable HCC
Malagari 2010[66]	DEB-TACE	TAE	HCC patients unsuitable for curative treatments, with potentially resectable lesions but at high risk for surgery and patients with HCC suitable for RFA but of high risk because of location
Brown 2016[67]	DEB-TACE	TAE	Adults with HCC with ECOG score of 0 to 1 and Okuda stage I or II

Risk of bias

Results of the risk-of-bias judgements are presented in *Appendix 5*.

The SorAfenib versus Radioembolization in Advanced Hepatocellular Carcinoma (SARAH) and Selective Internal Radiation Therapy Versus Sorafenib in Locally Advanced Hepatocellular Carcinoma (SIRveNIB) RCTs were both rated as having a low overall risk of bias.[19–21] There were some concerns regarding bias for the trials undertaken by Pitton *et al.*[23] and Kulik *et al.*[28] Concerns related to the randomisation process for the study by Pitton *et al.*[23] There were concerns related to the randomisation process, potential deviations from the intended interventions and measurement of the outcome for the study by Kulik *et al.*[28] The SIRTACE,[22] SORAMIC[24] and Prospective Randomized study of chEmoeMbolization versus radIoEmbolization for the tReatment of hEpatocellular carcinoma (PREMIERE)[25–27] trials were all rated as being at a high overall risk of bias; the SIRTACE trial was rated as being at a high risk of bias arising from the randomisation process, missing outcome data and measurement of the outcome,[22] the SORAMIC trial was rated as being at a high risk of bias in relation to deviations from the intended interventions as well as some concerns arising from the randomisation process,[24] and the PREMIERE trial was rated as being at a high risk of bias arising from the randomisation process and concerns arising from deviations from the intended interventions.[25–27]

The prospective comparative studies were all rated as being at a high risk of bias.[31–37] In particular, allocation to treatment groups was either inadequately described or inappropriate, resulting in differences in prognostic factors between treatment groups at baseline. Outcome assessors do not appear to have been blinded in any of the prospective comparative studies.

Four of the retrospective comparative studies were rated as being at a high risk of bias.[38–40,42] The two studies by Biederman *et al.*[38,39] appear to have included many of the same patients, although one of the studies was reported only as a conference abstract, with very limited study details.[38] Each of the studies rated as being at a high risk of bias appeared to include patients with different prognostic characteristics at baseline in the two different treatment groups. It was unclear whether or not outcome assessors were blinded in any of the studies. The study by Bhangoo *et al.*[41] was rated as being at an unclear risk of bias; it was unclear whether or not treatment groups were similar at baseline, whether or not outcome assessors were blinded and whether or not missing outcome data were balanced across treatment groups.

The small case series undertaken by Radosa *et al.*[51] should be considered to be at a high risk of bias; it is unclear whether or not patients were representative of all those who would be eligible for SIRT in clinical practice, outcome assessors were not blinded to the participants' intervention and outcome measures were not consistently assessed.

Efficacy and safety of SIR-Spheres

As discussed in *Study design*, RCTs were eligible for inclusion in the clinical effectiveness review, with non-randomised comparative studies and non-comparative studies considered for inclusion, in the absence of sufficient RCT evidence. Five RCTs of SIR-Spheres were identified, comparing SIR-Spheres with established therapies available to patients with intermediate (TACE/DEB-TACE) and advanced (sorafenib) HCC. Other studies of SIR-Spheres identified also compared with sorafenib or TACE (see *Table 3*); therefore, they were not included in the review.

This section focuses on the two large good-quality RCTs (SARAH and SIRveNIB) and also presents a brief summary of the three lower-quality RCTs of SIR-Spheres.

The SARAH and SIRveNIB randomised controlled trials

Two large RCTs compared SIR-Spheres with sorafenib in patients who were not suitable for curative treatments: the SARAH trial was conducted in France[19,20] and the SIRveNIB trial was conducted in the Asia-Pacific region.[21] Both trials were considered to have a low overall risk of bias (see *Appendix 5*). Further details of these trials are presented in *Table 5*.

As shown in *Table 5*, there were methodological differences between the SARAH and the SIRveNIB trials. In the SIRveNIB trial, patients could receive only one SIRT delivery, whereas in the SARAH trial patients could receive more than one delivery of SIRT; 69 out of 184 (37.5%) patients who received SIRT received more than one delivery to either the ipsilateral or the contralateral lobe.

The SARAH trial was conducted in France and the SIRveNIB trial was conducted in the Asia-Pacific region. This has implications for the generalisability of the SIRveNIB trial results to the UK population. HCC in European patients is more likely to be caused by alcohol or hepatitis C, whereas in Asia it is more likely to be caused by hepatitis B. The natural history of these diseases is different. Treatment options are also different, as hepatitis B-related liver disease is often less advanced than in alcohol-related or hepatitis C-related disease; therefore, patients may have had more treatment prior to receiving systemic therapy.

The Sirtex submission stated that patient selection in the SARAH trial did not reflect UK clinical practice, as the trial included patients with a poor survival prognosis who would be considered for only systemic therapy or BSC [e.g. because of a high tumour burden, main PVT or impaired liver function (Child–Pugh class B)]. Therefore, this has implications for the generalisability of the SARAH trial results to the UK population who would be eligible for SIRT in clinical practice.

In both trials, patients were assessed for suitability of SIRT after randomisation. In the SARAH trial, 53 out of 237 (22.4%) patients allocated to SIR-Spheres did not receive SIRT, 26 of whom were treated with sorafenib. In the SIRveNIB trial, 52 out of 182 (28.6%) patients allocated to SIR-Spheres

TABLE 5 Details of the SARAH and SIRveNIB RCTs

Characteristic	SARAH[19]		SIRveNIB[21]	
Trial characteristic				
Study design	Multicentre open-label RCT		Multicentre open-label RCT	
Location	France (25 centres)		Asia-Pacific region (11 countries)	
Source of funding	Sirtex		Sirtex	
Inclusion criteria	Locally advanced HCC (BCLC stage C) or new HCC not eligible for surgery/ablation after previously cured HCC (cured by surgery or thermoablative therapy) or HCC with two unsuccessful rounds of TACE. Life expectancy of > 3 months, ECOG performance status 0 or 1, Child–Pugh class A or B score of ≤ 7		Locally advanced HCC (BCLC stage B or C without extrahepatic disease) with or without PVT, not amenable to curative treatment modalities	
Intervention	SIR-Spheres ($n = 237$) Patients underwent angiography, protective coiling and MAA-SPECT/computerised tomography scan and were readmitted for SIRT 1 or 2 weeks later. In bilobar tumours, the first treatment was delivered to the hemiliver with the greatest tumour burden and the contralateral hemiliver was scheduled for treatment 30–60 days after the first treatment. If the tumour progressed, SIRT could be repeated 184/237 patients received SIR-Spheres: • One (unilobar) treatment = 115 patients • Two (ipsilateral) treatments = 17 patients • Two (contralateral) treatments = 41 patients • Three (ipsilateral) treatments = two patients • Three (contralateral) treatments = nine patients 53/237 (22%) patients did not receive SIRT		SIR-Spheres ($n = 182$) Patients underwent angiographic and MAA assessment of suitability for SIRT. Eligible patients received a single delivery of SIRT 52/182 (28.6%) patients did not receive SIRT	
Comparator	Sorafenib ($n = 222$) Continuous oral sorafenib (400 mg twice daily)		Sorafenib ($n = 178$) Continuous oral sorafenib (400 mg twice daily)	
Primary outcome	OS		OS	
Secondary outcomes	• PFS • Tumour response • Adverse events • Quality of life (EORTC QLQ-C30 version 3 and the specific HCC module QLQ-HCC18)		• PFS • Tumour response • Adverse events • Quality of life (EQ-5D)	
Baseline patient characteristic (ITT population)				
	SIR-Spheres	*Sorafenib*	*SIR-Spheres*	*Sorafenib*
Number of patients	237 (ITT) 174 (per protocol)	222 (ITT) 206 (per protocol)	182 (ITT) 130 (per protocol)	178 (ITT) 162 (per protocol)
Median/mean age (years)	66 (IQR 60–72)	65 (IQR 58–73)	59.5 (SD 12.9)	57.7 (SD 10.6)
Proportion male (%)	89	91	80.8	84.8

continued

TABLE 5 Details of the SARAH and SIRveNIB RCTs (*continued*)

Characteristic	SARAH[19]		SIRveNIB[21]	
Cirrhosis present, *n* (%)	211 (89)	201 (91)	NR	NR
Cause of HCC, *n* (%)				
Alcohol	147 (62)[a]	124 (56)[a]	NR	NR
Non-alcoholic steatohepatitis	49 (21)[a]	60 (27)[a]	NR	NR
Hepatitis B	13 (5)[a]	15 (7)[a]	93 (51.1)	104 (58.4)
Hepatitis C	55 (23)[a]	49 (22)[a]	26 (14.3)	19 (10.7)
Hepatitis B and C	NR	NR	4 (2.2)	5 (2.8)
Other/unknown	45 (19)[a]	41 (18)[a]	NR	NR
BCLC classification, *n* (%)				
Stage A	9 (4)	12 (5)	0	1 (0.6)
Stage B	66 (28)	61 (27)	93 (51.1)	97 (54.5)
Stage C	162 (68)	149 (67)	88 (48.4)	80 (44.9)
Child–Pugh classification, *n* (%)	A5 + A6: 196 (83)	A5 + A6: 187 (84)	A: 165 (90.7)	A: 160 (89.9)
	B7: 39 (16)	B7: 35 (16)	B: 14 (7.7)	B: 16 (9.0)
	Unknown: 2 (1)	Unknown: 0 (0)		
ECOG performance status, *n* (%)				
0	145 (61)	139 (63)	135 (74.2)	141 (79.2)
1	92 (39)	83 (37)	47 (25.8)	37 (20.8)
Tumours, *n* (%)				
Single	110 (46)	96 (43)	NR	NR
Multiple	127 (54)	126 (57)		
Tumour involvement, *n* (%)				
Unilobar	187 (79)	187 (84)	NR	NR
Bilobar	50 (21)	35 (16)		
MVI, *n* (%)	149 (63)	128 (58)	NR	NR
PVT, *n* (%)	NR	NR	56 (30.8)	54 (30.3)
Portal venous invasion, *n*/*N* (%)				
Main portal vein	49/143 (34)	38/118 (32)	NR	NR
Main portal branch (right or left)	65/143 (46)	59/118 (50)		
Segmental	29/143 (20)	21/118 (18)		
Portal vein occlusion, *n*/*N* (%)				
Complete	18/48 (38)	18/38 (47)	NR	NR
Incomplete	30/48 (62)	20/38 (53)		
Previously received TACE, *n* (%)	106/237 (45)	94/222 (42)	NR	NR

TABLE 5 Details of the SARAH and SIRveNIB RCTs (*continued*)

Characteristic	SARAH[19]		SIRveNIB[21]	
Trial results				
Median OS (months)	8.0 (95% CI 6.7 to 9.9)	9.9 (95% CI 8.7 to 11.4)	8.8	10.0
	HR 1.15, 95% CI 0.94 to 1.41; $p = 0.18$ (ITT)		HR 1.12, 95% CI 0.9 to 1.4; $p = 0.36$ (ITT)	
	HR 0.99, 95% CI 0.79 to 1.24 (per protocol)		HR 0.86, 95% CI 0.7 to 1.1; $p = 0.27$ (per protocol)	
Median PFS (months)	4.1 (95% CI 3.8 to 4.6)	3.7 (95% CI 3.3 to 5.4)	5.8	5.1
	HR 1.03, 95% CI 0.85 to 1.25; $p = 0.76$ (ITT)		HR 0.89, 95% CI 0.7 to 1.1; $p = 0.31$ (ITT)	
			HR 0.73, 95% CI 0.6 to 0.9; $p = 0.0128$ (per protocol)	
TTP (months)	NR		6.1	5.4
Tumour response rate	36/190 (19%) evaluable patients achieved a complete ($n = 5$) or partial ($n = 31$) response	23/198 (12%) evaluable patients achieved a complete ($n = 2$) or partial ($n = 21$) response	16.5% (all partial response, 0% achieved a complete response)	1.7% (all partial response, 0% achieved a complete response)
Rates of subsequent liver transplantation or resection	6/237 (2.5%) had tumour ablation[b]	2/222 (0.9%) had tumour ablation	1/182 (0.5%) had radiofrequency ablation	2/178 (1.1%) had radiofrequency ablation
	3/237 (1.3%) had liver surgery[b]	1/222 (0.5) had liver transplantation	2/182 (1.1%) had surgery	1/178 (0.6%) had surgery
	2/237 (0.8%) had liver transplantation			
HRQoL[c]	Global health status subscore was significantly better in the SIRT group than in the sorafenib group (group effect $p = 0.0048$; time effect $p < 0.0001$) and the between-group difference tended to increase with time (group × time interaction $p = 0.0447$)		There were no statistically significant differences in the EQ-5D index between the SIRT and sorafenib groups throughout the study in either the ITT or the per-protocol populations	
Number of patients reporting treatment-related adverse events, *n*/*N* (%)	173/226 (77)	203/216 (94)	78/130 (60)	137/162 (84.6)
Number of patients reporting grade ≥ 3 adverse events, *n*/*N* (%)	92/226 (41)	136/216 (63)	36/130 (27.7)	82/162 (50.6)

CI, confidence interval; EORTC QLQ, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D, EuroQol-5 Dimensions; HR, hazard ratio; IQR, interquartile range; ITT, intention to treat; MAA, macroaggregated albumin; NR, not reported; SD, standard deviation.

a The same patient could have several causes of disease.

b Further information provided by Sirtex in response to clarification questions stated that 7/237 patients had radiofrequency ablation and 4/237 patients had resection.

c HRQoL assessment had missing values for a high proportion of patients at most time points for SARAH and at some time points for SIRveNIB.

did not receive SIRT, three of whom were treated with sorafenib (where reported; subsequent treatments were not reported for 31/52 patients). Results were presented for both the intention-to-treat (ITT) and the per-protocol populations; patients who did not receive their allocated treatment were excluded from the per-protocol analysis (those who received sorafenib instead of SIRT were not included in the sorafenib arm in the per-protocol analysis).

The SARAH and SIRveNIB trial publications reported baseline characteristics for both the ITT and the per-protocol populations.[19,21] The SIR-Spheres and sorafenib groups were generally similar at baseline in the ITT populations (see *Table 5*). However, in the per-protocol population, patients in the sorafenib arm appeared to have slightly worse disease characteristics than those in the SIR-Spheres arm in the SARAH trial (BCLC stage C: 69.4% vs. 65.5%; Child–Pugh class B7: 14.6% vs. 11.5%; median tumour burden: 20% vs. 12.5%, respectively) and in the SIRveNIB trial (BCLC stage C: 45.1% vs. 38.5%; PVT: 29.6% vs. 23.1%; tumour size > 50% of liver: 21.6% vs. 17.7%, respectively).

Overall survival Neither trial found a statistically significant difference in OS between SIR-Spheres and sorafenib in either the ITT or the per-protocol analyses, as shown in *Table 5*.

Both trials undertook subgroup analyses according to baseline characteristics. The SIRveNIB trial reported a statistically significant difference in OS favouring SIR-Spheres in the subgroup of patients with BCLC stage C disease in the per-protocol analysis [median 9.2 vs. 5.8 months, hazard ratio (HR) 0.67, 95% confidence interval (CI) 0.4 to 1.0; $p = 0.0475$]. The SARAH trial demonstrated a statistically significant difference in OS favouring sorafenib in the subgroup of patients with complete occlusion in the main portal vein in the per-protocol analysis (HR 2.44, 95% CI 1.01 to 5.88); however, the number of patients included in this subgroup analysis was very small, so the result should be interpreted with caution.

Progression-free survival In the SARAH trial, PFS was defined as the time from the closest date of radiological examination before first administration of study treatment to disease progression, in accordance with Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 criteria,[68] or death. In the SIRveNIB trial, PFS was defined as the time from the date of randomisation to tumour progression at any site in the body, or death, whichever is earlier. Tumour progression was assessed in accordance with RECIST 1.1 criteria.[68]

Progression-free survival was not statistically significantly different between treatment groups in the ITT analyses of either the SARAH or the SIRveNIB trials. However, in the SIRveNIB trial, PFS was statistically significantly improved with SIR-Spheres in the per-protocol analysis (HR 0.73, 95% CI 0.6 to 0.9; $p = 0.0128$).

Tumour response rate Tumour response was statistically significantly greater in the SIR-Spheres arm than in the sorafenib arm in both the SARAH and the SIRveNIB trials (SARAH: 19% vs. 12%, $p = 0.0421$; SIRveNIB: 16.5% vs. 1.7%, $p < 0.001$). However, in the SARAH trial, only 190 SIR-Spheres patients and 198 sorafenib patients were evaluable and included in the analysis.

Rate of liver transplantation or resection A very small proportion of patients in both treatment arms of the SARAH and the SIRveNIB trials went on to have subsequent liver transplantation (< 1%), liver surgery (0.6–1.3%) or tumour ablation (0.5–2.5%).

Quality of life The SARAH trial reported statistically significantly better HRQoL in the SIR-Spheres treatment group than in the sorafenib group for both the ITT and the per-protocol populations, assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ)-C30. However, the proportion of patients who completed questionnaires was 71% in the SIR-Spheres group (169/237) and 84% (186/222) in the sorafenib group at baseline, reducing with time to only 29% (26/90 patients at risk) in the SIR-Spheres group and 32% (29/92 patients at risk) in the sorafenib group at 12-month follow-up. There was no statistically significant difference in HRQoL between the treatment groups in the SIRveNIB trial, assessed using the EuroQol-5 Dimensions (EQ-5D) index.

Adverse events The proportion of patients reporting at least one treatment-related adverse event (TRAE) and the proportion reporting at least one grade ≥ 3 adverse event (AE) was higher in the sorafenib group than in the SIR-Spheres group in both trials, as shown in *Table 5*.

In the SARAH trial, the most frequent grade ≥ 3 AEs were fatigue (SIR-Spheres 9% vs. sorafenib 19%), liver dysfunction (11% vs. 13%), increased laboratory liver values (9% vs. 7%), haematological abnormalities (10% vs. 14%), diarrhoea (1% vs. 14%), abdominal pain (3% vs. 6%), increased creatinine (2% vs. 6%) and hand–foot skin reaction (< 1% vs. 6%).

In the SIRveNIB trial, the most frequent grade ≥ 3 AEs of interest were anaemia (SIR-Spheres 0% vs. sorafenib 2.5%), fatigue (0% vs. 3.7%), diarrhoea (0% vs. 3.7%), abdominal pain (2.3% vs. 1.2%), ascites (3.8% vs. 2.5%), hypertension (0% vs. 1.2%), upper gastrointestinal haemorrhage (0.8% vs. 1.9%), jaundice (0.8% vs. 1.2%), radiation hepatitis (1.5% vs. 0%) and hand–foot skin reaction (0% vs. 16.7%).

The AE profiles of SIRT and sorafenib are very different. Sorafenib is a continuous treatment, whereas most patients receive only one delivery of SIRT [37.5% patients in the SARAH trial received more than one delivery, either to the ipsilateral or to the contralateral lobe (primarily because of bilobar tumours or a large central tumour requiring bilateral treatment), whereas in the SIRveNIB trial patients received only one delivery]. AE rates were not reported separately for patients who received more than one delivery of SIRT; therefore, it is not possible to compare AE rates for patients who received one delivery with those who received more than one delivery. In the SARAH trial, patients with bilobar tumours received the first treatment in the hemiliver with the greatest tumour burden, and treatment of the contralateral hemiliver was scheduled 30–60 days after the first treatment. No patient had a whole-liver treatment approach in one session. Clinical advisors confirmed that this is reflective of their experience; patients would not receive whole-liver treatment in one session to reduce the risk of radioembolisation-induced liver disease (REILD). However, the Sirtex submission states that SIR-Spheres can be administered to both lobes of the liver during the same procedure [based on observational data in which 95.9% patients in the European Network on Radioembolisation with Yttrium-90 Resin Microspheres (ENRY) register received whole-liver treatments in a single session[69]]; neither the SARAH trial nor the SIRveNIB trial administered SIR-Spheres to both lobes during the same procedure. This variance is probably because of the clinical indication for SIRT; the ENRY register is likely to include a majority of patients with colorectal cancer liver metastases, who do not have underlying cirrhosis, whereas in HCC patients the cirrhotic liver is likely to be more susceptible to REILD.

A relatively large proportion of patients who undergo work-up for SIRT, to assess their suitability for the procedure, are unable to receive SIRT (e.g. owing to liver-to-lung shunting or unfavourable hepatic arterial anatomy) [42/226 (18.6%) in SARAH and 37/182 (20.3%) in SIRveNIB]. The work-up of patients who are unable to undergo SIRT delivery has cost implications.

The SARAH randomised controlled trial subgroup analysis (low tumour burden/low albumin–bilirubin grade)

The Sirtex company submission selected a subgroup of patients from the SARAH trial with ≤ 25% tumour burden and albumin–bilirubin (ALBI) 1 for their base-case analysis in the economic model; the company stated that these patients are considered the most appropriate candidates for SIR-Spheres in clinical practice, as they are the most likely to benefit from SIRT. This is not a clinically recognised subgroup and was based on a post hoc analysis; therefore, these results should be prospectively validated before being considered relevant for clinical practice.

This subgroup included 37 (16%) patients in the SIRT group and 48 (22%) patients in the sorafenib group; 92% of those allocated to SIRT received treatment after work-up. Baseline characteristics were relatively well balanced between treatment groups, although more patients in the SIRT arm had BCLC stage B disease, single tumours and received previous TACE (these patients generally have a better

prognosis than patients who are diagnosed at a later stage and are not eligible for TACE) than in the sorafenib arm. More patients in the sorafenib arm had an ECOG performance status of 0 and unilobar liver involvement. *Table 6* presents the baseline characteristics and results for the full ITT population and the low tumour burden/low ALBI grade subgroup of the SARAH trial.

TABLE 6 Details of the ITT population and the low tumour burden/low ALBI grade subgroup of SARAH

	ITT population		Low tumour burden/ low ALBI grade subgroup	
Characteristic	**SIR-Spheres**	**Sorafenib**	**SIR-Spheres**	**Sorafenib**
Baseline patient characteristic				
Number of patients	237	222	37	48
Median age (years)	66	65	NR	NR
Age group (years) (%)				
≥ 65	NR	NR	43	48
< 65	NR	NR	57	52
BCLC classification (%)				
Stage A	4	5	3	6
Stage B	28	27	43	35
Stage C	68	67	54	58
Child–Pugh classification (%)	A5 + A6: 83	A5 + A6: 84	A: 95	A: 98
	B7: 16	B7: 16	B: 5	B: 2
	Unknown: 1	Unknown: 0		
ECOG performance status (%)				
0	61	63	62	79
1	39	37	38	21
Tumours (%)				
Single	46	43	43	33
Multiple	54	57	57	67
Tumour involvement (%)				
Unilobar	79	84	76	85
Bilobar	21	16	24	15
MVI (%)	63	58	54	52
Portal venous invasion, *n*/*N* (%)				
Main portal vein	49/143 (34)	38/118 (32)	11	10
Main portal branch	65/143 (46)	59/118 (50)		
Segmental	29/143 (20)	21/118 (18)		
Previously received TACE (%)	45	42	51	44

TABLE 6 Details of the ITT population and the low tumour burden/low ALBI grade subgroup of SARAH (*continued*)

Characteristic	ITT population		Low tumour burden/ low ALBI grade subgroup	
	SIR-Spheres	Sorafenib	SIR-Spheres	Sorafenib
Trial results				
Median OS (months)	8.0 (95% CI 6.7 to 9.9)	9.9 (95% CI 8.7 to 11.4)	21.9 (95% CI 15.2 to 32.5)	17.0 (95% CI 11.6 to 20.8)
	HR 1.15, 95% CI 0.94 to 1.41; $p = 0.18$		HR 0.73, 95% CI 0.44 to 1.21; $p = 0.22$	
Median PFS (months)	4.1 (95% CI 3.8 to 4.6)	3.7 (95% CI 3.3 to 5.4)	NR	NR
	HR 1.03, 95% CI 0.85 to 1.25; $p = 0.76$		HR 0.65, 95% CI 0.41 to 1.02; $p = 0.06$	
Tumour response rate	36/190 (19%) evaluable patients achieved a complete ($n = 5$) or partial ($n = 31$) response	23/198 (12%) evaluable patients achieved a complete ($n = 2$) or partial ($n = 21$) response	NR	NR
Rates of subsequent liver transplantation or resection	6/237 (2.5%) had tumour ablation[a]	2/222 (0.9%) had tumour ablation	14% (subsequent curative therapy)	2% (subsequent curative therapy)
	3/237 (1.3%) had liver surgery[a]	1/222 (0.5%) had liver transplantation		
	2/237 (0.8%) had liver transplantation			
HRQoL[b]	Global health status subscore was significantly better in the SIRT group than in the sorafenib group (group effect $p = 0.0048$; time effect $p < 0.0001$) and the between-group difference tended to increase with time (group*time interaction $p = 0.0447$)		NR	
Number of patients reporting TRAEs, *n/N* (%)	173/226 (77)	203/216 (94)	NR	NR
Number of patients reporting grade ≥ 3 AEs, *n/N* (%)	92/226 (41)	136/216 (63)	NR	NR

NR, not reported.
a Further information provided by Sirtex in response to clarification questions stated that 7/237 patients had radiofrequency ablation and 4/237 patients had resection.
b HRQoL assessment had missing values for a high proportion of patients at most time points for SARAH and at some time points for SIRveNIB.

As shown in *Table 6*, median OS and PFS appeared to be better in the SIR-Spheres arm than in the sorafenib arm in the post hoc subgroup analysis, although the difference between treatment groups was not statistically significant. The proportion of patients who went on to have potentially curative therapy was higher in the SIR-Spheres arm than in the sorafenib arm, although numbers were very low (five and one patients, respectively). Tumour response rate, HRQoL and AEs were not reported separately for the low tumour burden/low ALBI grade subgroup.

Prespecified and post hoc subgroup analysis results were presented in the SARAH trial publication for OS.[19] Tumour burden was included as a post hoc subgroup. However, neither the ALBI grade nor the combination of low tumour burden and low ALBI grade was presented.

The SIRveNIB trial did not report subgroup analysis results for the subgroup of low tumour burden/low ALBI grade patients. However, ALBI grade was included in the OS subgroup analysis. Results favoured

SIR-Spheres in the subgroup of ALBI 1 patients (HR 0.89, 95% CI 0.6 to 1.4; $p = 0.58$), whereas results favoured sorafenib for the subgroup of patients with ALBI 2/3 (HR 1.24, 95% CI 0.9 to 1.7; $p = 0.14$).

Other randomised controlled trials of SIR-Spheres

The SIRTACE is a small RCT rated as being at a high risk of bias that compared SIR-Spheres ($n = 13$) with TACE ($n = 15$) in patients with unresectable HCC without portal vein occlusion.[22] A higher proportion of patients in the SIRT group had BCLC stage A disease (38.5% vs. 26.7%) and Child–Pugh liver function class A (92.3% vs. 86.7%) than in the TACE group. The average number of tumour nodules was higher in the TACE group (5.0 vs. 3.5). Therefore, patients in the SIR-Spheres treatment arm had a better prognosis than those in the TACE arm.

At 6 months, 69.2% of SIRT patients and 86.7% of TACE patients were still alive. At 12 months, 46.2% of SIRT patients and 66.7% of TACE patients were still alive. PFS, disease control rate and the proportion of patients who went on to have potentially curative therapy were similar between treatment groups. The proportion of patients with a partial response was higher in the SIRT group than in the TACE group (30.8% vs. 13.3%), although patient numbers were very small.

There were no statistically significant differences between treatment groups in HRQoL by week 12, despite Functional Assessment of Cancer Therapy Hepatobiliary-Pancreatic Symptom Index (FACT-Hep) scores being lower in the SIRT group at baseline (indicating lower quality of life). However, 10 out of 28 patients had missing baseline data and were excluded from HRQoL analyses. The proportion of patients reporting TRAEs was higher in the TACE group than in the SIRT group (33.3% vs. 23.1%), although the proportion of patients reporting at least one AE was higher in the SIRT group (92.3% vs. 66.7%), as was the number of patients with grade ≥ 3 AEs (three vs. two patients) and serious AEs requiring hospitalisation (seven vs. five patients).

A small RCT by Pitton *et al.*,[23] with some concerns regarding bias, compared SIR-Spheres ($n = 12$) with DEB-TACE ($n = 12$) in patients with unresectable intermediate (BCLC stage B) HCC with preserved liver function (Child–Pugh class A–B7). Treatment groups appeared reasonably similar at baseline, although more patients in the SIRT group had received prior local ablation (four vs. one) and more patients in the DEB-TACE group had received prior resection (five vs. three). Median OS and PFS were longer in the DEB-TACE arm than in the SIR-Spheres arm (788 days vs. 592 days and 216 days vs. 180 days, respectively), although the difference between groups was not statistically significant. Median TTP was 371 days in the SIRT arm and 336 days in the DEB-TACE arm. AEs were not reported.

The SORAMIC RCT compared SIR-Spheres followed by sorafenib with sorafenib alone in patients with unresectable intermediate or advanced (BCLC stage B or C) HCC with preserved liver function (Child–Pugh class $\leq$ B7) and ECOG performance status of < 2, who were poor candidates for TACE. Only safety and tolerability data for the first 40 patients have been published to date, rated as being at a high risk of bias.[24] More patients in the sorafenib-alone group had PVT (35% vs. 15%) and BCLC stage C disease (70% vs. 60%), indicating poorer prognosis in this group. There were 196 treatment-emergent AEs reported in the SIRT plus sorafenib arm and 222 events in the sorafenib-alone arm, of which 21.9% and 21.2%, respectively, were considered to be grade ≥ 3. The most common grade 3 or 4 AEs (hypertension, hand–foot skin reaction and diarrhoea) were reported in a similar number of patients in both treatment arms. Grade 3 or 4 fatigue appeared more common in patients receiving SIRT plus sorafenib (20% vs. 10%). Grade 3 or 4 infection and anorexia appeared more common in patients receiving sorafenib alone (20% vs. 5% and 0% vs. 10%, respectively). Grade 3 or 4 laboratory-related events were more common in patients receiving sorafenib alone (elevated gamma-glutamyltransferase level 45% vs. 30%, elevated aspartate aminotransferase level 15% vs. 0% and elevated alanine aminotransferase level 10% vs. 0%). One patient experienced a grade 3 gastric ulcer that was probably (but not proven to be) related to SIRT microspheres deposition.

Further details of each of these trials are presented in *Appendix 6*.

Ongoing studies

There are three ongoing studies of SIR-Spheres including patients with HCC: the Austrian Cardiovascular and Interventional Radiological Society of Europe Registry for SIR-Spheres Therapy (CIRT),[70] the RESIN tumour registry in the USA[71] and the RESIN tumour registry in Taiwan.[72] The CIRT study was completed in January 2020, the RESIN tumour registry study in the USA is due to be completed in August 2022 and the RESIN tumour registry study in Taiwan was due to be completed in December 2019.

There is also an ongoing individual patient data prospective meta-analysis of patients from the SIRveNIB and SARAH trials: VESPRO.[73]

Efficacy and safety of TheraSphere

As discussed in *Study design*, RCTs were eligible for inclusion in the clinical effectiveness review. Non-randomised comparative studies (including retrospective studies) and non-comparative studies were considered for inclusion in the absence of sufficient RCT evidence. Only two small RCTs of TheraSphere were identified. Therefore, prospective non-randomised comparative studies were also included in the clinical effectiveness review; seven non-RCTs were included, most of which compared TheraSphere with TACE/DEB-TACE. The retrospective comparative studies of TheraSphere that were identified also compared against TACE/DEB-TACE (see *Table 3*); therefore, they were not included in the review as they were considered to be lower quality than the prospective comparative studies.

One small RCT rated as being at a high risk of bias (PREMIERE) compared TheraSphere ($n = 24$) with TACE ($n = 21$) as a bridge to transplant in patients with BCLC stage A or B unresectable HCC with no vascular invasion and Child–Pugh liver function class A or B.[25–27] The proportion of patients with Child–Pugh class A was much higher in the TACE arm than in the TheraSphere arm (71% vs. 50%) and the proportion of patients with portal hypertension was much lower in the TACE arm (52% vs. 83%), suggesting better prognosis in the TACE arm. OS was slightly longer in the TheraSphere arm (18.6 months vs. 17.7 months) and the rate of liver transplant/resection was also higher in the TheraSphere arm (87% vs. 70% of 'listed patients'), although time to transplant/resection was slightly longer in the TheraSphere arm (8.8 months vs. 7.6 months). TTP was significantly longer in the TheraSphere arm: overall median TTP was not reached in the TheraSphere arm (> 26 months) and was 6.8 months in the TACE arm (HR 0.112, 95% CI 0.027 to 0.557; $p = 0.007$); TTP in the non-transplanted patients was also significantly longer in the TheraSphere arm (median > 26 months vs. 4.8 months). AEs and HRQoL were not reported.

One small RCT by Kulik *et al.*,[28–30] which caused some concerns regarding bias, compared TheraSphere plus sorafenib ($n = 10$) with sorafenib alone ($n = 10$) as a bridge to transplant in patients with Child–Pugh liver function class ≤ B8 HCC who were potential candidates for liver transplant. A higher proportion of patients in the TheraSphere plus sorafenib arm were male (80% vs. 50%) and had BCLC stage A disease (70% vs. 50%), with more patients in the TheraSphere-alone arm having BCLC stage C disease (40% vs. 20%). More patients in the TheraSphere plus sorafenib arm had ECOG performance status 0 (80% vs. 60%) and Child–Pugh liver function class A (80% vs. 60%). Three patients died in the TheraSphere arm, compared with two patients in the TheraSphere plus sorafenib arm. The proportion of patients receiving liver transplant or resection was 90% in each treatment arm. Most AEs were more common in the TheraSphere-alone arm (fatigue 90% vs. 40%, diarrhoea 20% vs. 10%, pain 50% vs. 0%, nausea 70% vs. 20% and vomiting 20% vs. 0%), although grade ≥ 3 hand–foot skin reaction was more common in the TheraSphere plus sorafenib arm (20% vs. 0%).

Five prospective comparative studies, all rated as being at a high risk of bias, compared TheraSphere with TACE/DEB-TACE in patients with HCC.[31–35] Two studies assessed OS. In one small study ($n = 86$), OS appeared slightly longer with TACE than with TheraSphere in patients with intermediate-stage disease (median 18 months vs. 16.4 months).[32] In a much larger study ($n = 765$) in which survival outcomes were stratified by BCLC stage and Child–Pugh liver function class, survival was longer in the TACE arm for patients with early- and intermediate-stage disease but longer in the TheraSphere arm for patients with advanced-stage disease.[35] Two small studies ($n = 86$ and $n = 96$) assessed TTP, which

was longer with TheraSphere than with TACE (median 13.3 months vs. 6.8 months and median 13.3 months vs. 8.4 months).[32,34] Two small studies ($n = 67$ and $n = 86$) assessed complete or partial response rate; results were conflicting, with one study[31] favouring TACE (2.3% vs. 0%, using RECIST criteria[68]) and the other[32] favouring TheraSphere (75% vs. 50%, using modified RECIST criteria[68]). Two small studies ($n = 67$ and $n = 56$) assessed HRQoL, both favouring TheraSphere.[31,33] Only one study ($n = 86$) reported AEs; the most commonly reported AE (unspecific abdominal pain) was more frequent in TACE patients than in SIRT patients (83% vs. 5%).[32]

One small prospective matched case–control study by Maccauro *et al.*,[36] rated as being at a high risk of bias, compared TheraSphere plus sorafenib ($n = 15$) with TheraSphere alone ($n = 30$) in patients with predominantly BCLC stage C (due to PVT) unresectable HCC with Child–Pugh liver function class A. The study was published only as a conference abstract; therefore, very limited data are available. Results were similar between treatment groups for OS (median 10 months in each treatment arm), PFS (median 6 months vs. 7 months in the TheraSphere plus sorafenib and TheraSphere-alone arms, respectively) and response rate, using modified RECIST criteria[68] (45.5% vs. 42.8%). However, response rate using EASL criteria[1] was better in the TheraSphere-alone arm (40% vs. 10%).

One small prospective comparative study by Woodall *et al.*,[37] rated as being at a high risk of bias, compared TheraSphere in HCC patients without PVT ($n = 20$) with TheraSphere in HCC patients with PVT ($n = 15$) and a no-treatment control (BSC) in HCC patients who were not eligible for SIRT owing to substantial extrahepatic disease or hepatopulmonary shunt or underlying liver insufficiency ($n = 17$). OS was significantly longer in patients without PVT who received TheraSphere (median 13.9 months) than in patients with PVT who received TheraSphere (median 3.2 months) and patients who received BSC (median 5.2 months). AEs were more common in TheraSphere patients who had PVT than in those who did not have PVT (33% vs. 25%). No other outcomes were reported.

Further details of each of these studies are presented in *Appendix 6*.

Ongoing studies

There is one ongoing RCT of TheraSphere in patients with HCC: STOP-HCC, which has an estimated study completion date of February 2020; final results are not anticipated before at least December 2020.[74]

The BTG submission presents 12 additional ongoing or planned studies of TheraSphere.

Efficacy and safety of QuiremSpheres

Only one study of QuiremSpheres has been completed in patients with HCC: a small case series undertaken by Radosa *et al.*[51] Nine patients with HCC were retrospectively identified from a prospectively maintained database of patients who received QuiremSpheres between March 2017 and April 2018 at a single centre. It is unclear whether or not patients were representative of all those who would be eligible for SIRT in clinical practice. The available data are too limited to draw any conclusions about the safety or efficacy of QuiremSpheres. Study details are presented in *Appendix 6*.

Ongoing studies

There are three ongoing studies of QuiremSpheres including patients with HCC: HEPAR Primary,[75] HORA EST HCC[76] and Hope166.[77] All three studies are currently recruiting patients.

Direct comparisons of different selective internal radiation therapies

Five small retrospective comparative studies, all rated as being at a high or unclear risk of bias, compared SIR-Spheres with TheraSphere. No studies were identified that directly compared QuiremSpheres with either SIR-Spheres or TheraSphere. Further details of each of the five studies are presented in *Appendix 6*. The two studies by Biederman *et al.* ($n = 97$[38] and $n = 90$[39]) included patients who all had PVT and appear to have included some of the same patients, although one of the studies was published only

as a conference abstract,[38] so it is unclear how much overlap there was. The study by d'Abadie *et al.*[42] ($n = 58$ procedures) aimed to investigate the difference in efficacy per Gy of resin versus glass spheres and whether or not the difference could result from the different degrees of heterogeneity in sphere distribution; limited patient outcomes were reported.

Overall survival was reported in four studies [$n = 97$,[38] $n = 90$ (possibly with some overlap),[39] $n = 77$[40] and $n = 17$[41]]. OS was longer in the TheraSphere arm in three of the studies,[38,39,41] two of which included patients who all had PVT.[38,39] Median OS in the SIR-Spheres arm ranged from 3.7 to 7.7 months. Median OS in the TheraSphere arm ranged from 7.0 to 15 months.

Progression-free survival was reported in only one study ($n = 77$), in which it was longer in the SIR-Spheres arm (6.1 months vs. 5.0 months).[40] However, TTP was reported for the two treatment arms separately in one other study ($n = 90$ patients with PVT), in which it was longer in the TheraSphere arm (5.9 months vs. 2.8 months).[39]

Tumour response rate was reported for the two treatment arms separately in only one study ($n = 90$ patients with PVT), in which a higher proportion of evaluable patients had a complete (8.8% vs. 0%) or partial (31.6% vs. 13.3%) response in the TheraSphere arm.[39]

None of the studies reported HRQoL outcomes.

Adverse events were reported separately for the two treatment arms in two studies. The study by Biederman *et al.*[39] ($n = 90$ patients with PVT) reported no significant difference in pain (41.2% vs. 30.8%), fatigue (17.6% vs. 18.5%), nausea (17.6% vs. 3.1%) or anorexia (0% vs. 9.2%) between the SIR-Spheres and TheraSphere arms, respectively. In the very small study by Bhangoo *et al.*[41] ($n = 17$), all clinical toxicities reported were more frequent in the SIR-Spheres arm than in the TheraSphere arm (fatigue 67% vs. 45%, abdominal pain 33% vs. 27%, nausea/vomiting 67% vs. 55%, anorexia/weight loss 33% vs. 9%, diarrhoea 17% vs. 0% and gastric ulcer 17% vs. 0%).

An addendum, in the form of an academic-in-confidence manuscript, was received from Terumo Europe NV (hereafter Terumo) in August 2019. The manuscript described a retrospective pilot study of (confidential information has been removed) patients treated with QuiremSpheres, TheraSphere or SIR-Spheres at two centres in Germany and the Netherlands. OS and response were assessed at 6 months for all three interventions and at 12 months for QuiremSpheres and SIR-Spheres. Median OS was similar between the treatment groups at 6 months (confidential information has been removed) and 12 months (confidential information has been removed). The most commonly reported AEs were (confidential information has been removed) abdominal pain, fatigue and nausea; other AEs were rarely reported. This was a very small pilot study with unclear patient selection; patients in the TheraSphere group had poorer prognosis at baseline than did the other two treatment groups. The authors acknowledge that the study carries several methodological limitations.[78]

Clinical effectiveness summary and conclusions

SIR-Spheres

There are two large good-quality RCTs comparing SIR-Spheres with sorafenib (SARAH[19,20] and SIRveNIB[21]).

There was no statistically significant difference in OS (HR 1.15, 95% CI 0.94 to 1.41 SARAH, and HR 1.12, 95% CI 0.9 to 1.4 SIRveNIB) or PFS (HR 1.03, 95% CI 0.85 to 1.25 SARAH, and HR 0.89, 95% CI 0.7 to 1.1 SIRveNIB) in the SARAH or SIRveNIB trials in the ITT populations. However, tumour response rate was significantly greater in the SIR-Spheres arm than in the sorafenib arm in both trials (of patients who were evaluable and included in the analyses). The SARAH trial reported significantly better HRQoL in the SIR-Spheres arm than in the sorafenib arm, assessed using the EORTC QLQ-C30,

although the proportion of patients who completed the questionnaires was low, particularly at later time points. The SIRveNIB trial found no significant difference in HRQoL assessed using the EQ-5D index. The AE profiles of SIR-Spheres and sorafenib are very different, although the most common AEs generally occurred more frequently in the sorafenib arm in both trials.

There are some concerns regarding the generalisability of the SARAH and SIRveNIB trials to patients who would be eligible for SIRT in UK practice. The SIRveNIB trial was conducted in the Asia-Pacific region, where the aetiology of HCC differs from that in European patients; HCC is predominantly caused by hepatitis B in Asia, whereas it is predominantly caused by alcohol or hepatitis C in Europe. The SARAH trial included patients with a poorer prognosis than those who would be considered for SIRT in UK practice (e.g. high tumour burden, main PVT or impaired liver function).

Around one-fifth of patients in the SARAH and SIRveNIB trials were not suitable for SIRT after work-up (e.g. due to liver-to-lung shunting or unfavourable hepatic arterial anatomy); a proportion of patients assessed for suitability for SIRT in clinical practice would also be considered unsuitable, with associated cost implications.

Patients with bilobar disease may require more than one administration of SIRT. In the SARAH trial, patients with bilobar tumours received the first treatment in the hemiliver with the greatest tumour burden, and treatment of the contralateral hemiliver was scheduled 30–60 days after the first treatment. However, the Sirtex submission states that SIR-Spheres can be administered to both lobes of the liver during the same procedure; neither the SARAH trial nor the SIRveNIB trial administered SIR-Spheres to both lobes during the same procedure. Clinical advisors confirmed that this is reflective of their experience, in which patients would not receive whole-liver treatment in one session to reduce the risk of REILD.

The Sirtex company submission selected a subgroup of patients from the SARAH trial with $\leq$ 25% tumour burden and ALBI 1 for its base-case analysis in the economic model; the company stated that these patients are considered the most appropriate candidates for SIR-Spheres in clinical practice, as they are the most likely to benefit from SIRT. This is not a clinically recognised subgroup and was based on a post hoc analysis; therefore, these results should be prospectively validated before being considered relevant to clinical practice. Median OS (HR 0.73, 95% CI 0.44 to 1.21) and PFS (HR 0.65, 95% CI 0.41 to 1.02) appeared better in the SIR-Spheres arm than in the sorafenib arm in the subgroup analysis, although the difference between treatment groups was not statistically significant. The proportion of patients who went on to have potentially curative therapy was higher in the SIR-Spheres arm than in the sorafenib arm, although numbers were very low (five and one patients, respectively).

Three very small poorer-quality RCTs compared SIR-Spheres with TACE,[22] DEB-TACE[23] or SIR-Spheres plus sorafenib versus sorafenib alone.[24] The trials comparing SIR-Spheres with TACE or DEB-TACE appeared to favour the chemoembolisation procedure over SIRT in terms of survival outcomes.[22,23] The addition of SIR-Spheres to sorafenib did not appear to increase the number of treatment-emergent AEs.[24]

TheraSphere

Two small RCTs[25–30] and seven prospective comparative studies[31–37] of TheraSphere were included in the clinical effectiveness review; one of the RCTs (PREMIERE) and all of the non-RCT studies were rated as being at a high risk of bias, and the other RCT caused some concerns regarding bias. Therefore, all of these results should be interpreted with caution.

Both RCTs assessed TheraSphere as a bridge to transplant. The PREMIERE RCT reported longer TTP, a higher proportion of patients undergoing transplant and slightly longer OS in the TheraSphere arm than in the TACE arm.[25–27] Kulik *et al.*[28–30] reported similar survival and transplant/resection rates between patients receiving TheraSphere plus sorafenib or sorafenib alone.

Five prospective comparative studies compared TheraSphere with TACE or DEB-TACE; OS appeared better with TheraSphere in patients with early- and intermediate-stage disease.[32,35] TTP was longer with TheraSphere than with TACE.[32,34] Results relating to response rates were conflicting.[31,32] HRQoL appeared better with TheraSphere.[31,33] One study reported that the most common AE was more frequent with TACE than with SIRT.[32]

One prospective comparative study compared TheraSphere plus sorafenib with TheraSphere alone, with similar results between treatment groups.[36] The other study compared TheraSphere in patients with or without PVT with no treatment in patients unsuitable for TheraSphere; OS was significantly longer in patients without PVT who received TheraSphere compared with those with PVT who received TheraSphere and those who received only BSC.[37]

QuiremSpheres

Only one study of QuiremSpheres has been completed in patients with HCC: a small case series undertaken by Radosa *et al.*[51] The available data are too limited to draw any conclusions about the safety or efficacy of QuiremSpheres.

Direct comparison of different selective internal radiation therapies

Five small retrospective comparative studies, all rated as being at a high or unclear risk of bias, compared SIR-Spheres with TheraSphere. Two of the studies included patients who all had PVT and appear to have included some of the same patients.[38,39] OS was reported in four studies, including the two studies of patients with PVT; OS was longer in the TheraSphere arm in three of the studies.[38,39,41] One study assessed PFS, which was longer with SIR-Spheres,[40] and another study assessed TTP, which was longer with TheraSphere (in patients with PVT).[39] Tumour response rate was higher in the TheraSphere arm than in the SIR-Spheres arm in patients with PVT.[39] One very small study reported more frequent clinical toxicities in the SIR-Spheres arm than in the TheraSphere arm.[41] In patients with PVT, there was no difference in the frequency of fatigue, but pain and nausea appeared more frequent with SIR-Spheres, and anorexia appeared more frequent with TheraSphere.[39]

No studies were identified that directly compared QuiremSpheres with either SIR-Spheres or TheraSphere.

The BTG submission described a systematic review by Kallini *et al.*,[79] supported by funding from BTG, which aimed to compare the AE profiles of TheraSphere and SIR-Spheres for the treatment of unresectable HCC. Twenty-two observational studies of TheraSphere and nine observational studies of SIR-Spheres were included in the review and the number of AEs and number of patients across studies were summed to calculate the proportion of patients experiencing each AE. No studies directly comparing TheraSphere with SIR-Spheres were included in the review. AE reporting appears to have been variable between studies, with many AEs being reported by very few of the included studies (e.g. hepatobiliary and respiratory AEs). Baseline characteristics of patients were poorly reported in many of the included studies. Gastric ulcers were reported more frequently with SIR-Spheres than with TheraSphere [3.1% (six studies) vs. 0.1% (nine studies)], but the proportion of patients reporting ascites was higher with TheraSphere than with SIR-Spheres [9.2% (10 studies) vs. 4.7% (5 studies)]. Nausea (13 studies in total), fatigue (16 studies in total) and abdominal pain (18 studies in total) occurred in similar proportions of patients for both interventions.[79]

An addendum, in the form of an academic-in-confidence manuscript, was received from Terumo in August 2019. OS and response were similar between the treatment groups. The most commonly reported AEs were (confidential information has been removed) abdominal pain, fatigue and nausea; other AEs were rarely reported. This was a very small pilot study with several methodological limitations.[78]

Conclusions

There is a large body of evidence on the clinical effectiveness and safety of SIRT compared with sorafenib or TACE. Only two studies were considered to have a low risk of bias: SARAH[19,20] and

SIRveNIB,[21] which both compared SIR-Spheres with sorafenib. However, there are some concerns regarding the generalisability of the results of these two RCTs to the UK HCC population, particularly the SIRveNIB trial, which was conducted in the Asia-Pacific region where the aetiology of HCC differs from that in Europe.

Both RCTs found no significant difference in OS or PFS between SIR-Spheres and sorafenib, despite statistically significantly greater tumour response rate in the SIR-Spheres arm of both trials. The SARAH trial reported a significant difference between groups in HRQoL, favouring SIR-Spheres; however, the proportion of patients who completed the questionnaires was low. AEs, particularly grade ≥ 3 events, were more frequent in the sorafenib group in both trials.

The Sirtex company submission selected a subgroup of patients from the SARAH trial with $\leq 25\%$ tumour burden and ALBI 1 for its base-case analysis in the economic model. Although results appeared more promising in this subgroup of patients with a better prognosis, these post hoc subgroup analysis results should be prospectively validated before being considered relevant to clinical practice.

In studies comparing the different SIRT, patients with PVT appeared to have better survival outcomes with TheraSphere than with SIR-Spheres; however, this result was from a small retrospective comparative study rated as being at a high risk of bias and, therefore, may not be reliable. Other studies comparing TheraSphere with SIR-Spheres that did not include only patients with PVT had conflicting results. The only study that compared QuiremSpheres with SIR-Spheres and TheraSphere was provided by Terumo as an addendum in August 2019. Clinical outcomes appeared to be similar between treatment groups; however, this was a very small pilot study with several methodological limitations.

Chapter 4 Evidence synthesis to inform the relative efficacy of the interventions

Overview

Studies assessing the clinical effectiveness of SIRT for patients with unresectable HCC have been discussed and summarised in *Chapter 3*. The PRISMA flow diagram describing the selection process is shown in *Figure 1*. Treatment options vary greatly for patients with unresectable HCC according to the stage and severity of cancer and liver disease, as described in *Chapter 1*, *Current service provision*. Therefore, three NMA models were produced to represent the different populations of unresectable HCC patients. The 26 comparative studies and RCTs included in the systematic review of clinical effectiveness (see *Table 3*) and the 11 RCTs of CTTs (see *Table 4*) were screened for inclusion in each of the three NMA models. Alongside this, two studies of systemic therapies were identified from recent NICE single technology appraisals of sorafenib and lenvatinib: Llovet *et al.*[80] and Kudo *et al.*[81] Therefore, 39 studies were screened for inclusion in each of the three NMAs.

Network meta-analysis of adults with unresectable hepatocellular carcinoma who are eligible for transplant and of those eligible for conventional transarterial therapies

Meta-analysis using mixed treatment comparisons enables the estimation of different parameters when direct evidence on comparisons of interest is absent or sparse. The statistical synthesis method of NMA enables the comparison of multiple treatment options using both direct comparisons of interventions from RCTs and indirect comparisons across trials based on a common comparator.[82] As suggested by the term, NMA needs a 'network of evidence' to be established between all the interventions of interest.

Network 1: adults with unresectable hepatocellular carcinoma who are eligible for transplant

The first model (network 1) included patients with early/intermediate-stage unresectable HCC who were eligible for transplant. SIRT could potentially be used as a bridging treatment for patients awaiting transplant as described in *Chapter 1*, *Description of the technology under assessment*. These patients are generally classed as BCLC stage A patients, with preserved liver function and performance status 0–1. To ensure consistency in the compared studies, studies were included only if ≥ 70% of the recruited population had early-stage HCC or if results were split by disease stage. Only 2 out of 39 studies were selected for network 1. This included two small RCTs: PREMIERE[25] and Kulik *et al.*[28] The main reason for the exclusion of studies was patients having advanced-stage disease and, therefore, not being eligible for transplant. The reasons for including and excluding each study are reported in *Table 7*.

However, clinical advice was that there are short transplant waiting times in the UK (< 2 months), whereas the two trials in the network had transplant waiting times of roughly 7–9 months (mean 7.8 months in Kulik *et al.*[28] and median 8.8 months in Salem *et al.*[25]). Therefore, the network may not be generalisable to the UK and there may be limited opportunity for benefit in the UK given the short waiting times. Clinicians advised that, in the UK, bridging treatment is also used during the work-up phase, before the patient goes on to the waiting list. However, TACE rather than SIRT is more commonly used in this context. Furthermore, the two RCTs included in the network have very small sample sizes and, therefore, any efficacy estimates produced would be highly uncertain. Therefore, network 1, of patients with early/intermediate-stage HCC, was not conducted as it was deemed unsuitable for decision-making.

TABLE 7 Network 1: adults with unresectable HCC who are potentially eligible for transplant

Study (first author and year)	*n*	Intervention	Comparator	Study design	Reason for inclusion/exclusion
Studies included in the network (n = *2*)					
Salem 2016[25–27] (PREMIERE)	45	TheraSphere	TACE	RCT	Patients with early/intermediate HCC with no vascular invasion. The intent of therapy was bridge to transplant
Kulik 2014[28]	20	TheraSphere	TheraSphere plus sorafenib	RCT	Adults with Child–Pugh class ≤ B8 and potential candidates for orthotopic liver transplant. BCLC stage C patients (30%) were symptomatic only
Studies excluded from this network (n = *37*)					
Kolligs 2015[22] (SIRTACE)	28	SIR-Spheres	TACE	RCT	Mixed population of early- and intermediate-stage patients, without portal vein occlusion. Pilot trial funded by Sirtex. Results split for transplantable patients were requested but not provided
Chow 2018[21] (SIRveNIB)	360	SIR-Spheres	Sorafenib	RCT	Adults with locally advanced HCC (BCLC B or C) not amenable to curative treatment
Vilgrain 2017[19,84] (SARAH)	459	SIR-Spheres	Sorafenib	RCT	Adults with locally advanced HCC (BCLC C) or new HCC not eligible for surgery/ablation after previously cured HCC or HCC with two unsuccessful rounds of TACE. Only a few patients received curative therapy
Pitton 2015[23]	24	SIR-Spheres	DEB-TACE	RCT	Adults with intermediate-stage HCC (BCLC stage B). Patients eligible for curative therapy were excluded
Ricke 2015[24] (SORAMIC)	40	SIR-Spheres plus sorafenib	Sorafenib	RCT	Adults with unresectable intermediate or advanced HCC (BCLC stage B or C). No patients received transplant
Kudo 2018[81] (REFLECT)	289 (subgroup of 954 patients)	Lenvatinib	Sorafenib	RCT	Subgroup of adults with advanced-stage HCC, majority had PVI or extrahepatic spread – ineligible for transplant
Llovet 2008[80] (SHARP)	602	Sorafenib	Placebo	RCT	Adults with intermediate- and advanced-stage HCC, majority had extrahepatic spread/ vascular invasion. Patients ineligible for transplant
Malagari 2010[66]	87	DEB-TACE	TAE	RCT	Patients unsuitable for curative treatments with potentially resectable lesions but at high risk for surgery
Brown 2016[67]	101	DEB-TACE	TAE	RCT	Mixed population and some patients with PVI, ineligible for transplant

TABLE 7 Network 1: adults with unresectable HCC who are potentially eligible for transplant (*continued*)

Study (first author and year)	*n*	Intervention	Comparator	Study design	Reason for inclusion/exclusion
Lammer 2010[56,57] (PRECISION)	212	DEB-TACE	TACE	RCT	No relevant outcomes reported
Golfieri 2014[58]	177	DEB-TACE	TACE	RCT	Adults with early-, intermediate- and advanced-stage HCC without PVT. The population is too varied to include
Sacco 2011[59]	67	DEB-TACE	TACE	RCT	Patients with early- and intermediate-stage HCC, ineligible for transplant
van Malenstein 2011[60]	30	DEB-TACE	TACE	RCT	No relevant outcomes reported
Llovet 2002[61]	112	TACE	TAE	RCT	Adults with intermediate- and advanced-stage HCC, ineligible for transplant
Kawai 1992[62]	289	TACE	TAE	RCT	Patients with early/ intermediate-stage HCC but no relevant transplant results reported
Chang 1994[63]	46	TACE	TAE	RCT	Patients with inoperable HCC
Meyer 2013[64]	86	TACE	TAE	RCT	Patients with early-, intermediate- and advanced-stage HCC, ineligible for transplant
Yu 2014[65]	98	TACE	TAE	RCT	Adults with early-, intermediate- and advanced-stage HCC, ineligible for transplant
Kirchner 2019[31]	94	TheraSphere	TACE/ DEB-TACE	Prospective comparative	No relevant outcomes reported
Hickey 2016[35]	765	TheraSphere	TACE	Prospective comparative	Includes patients potentially eligible for transplant, but no transplant outcomes were reported
El Fouly 2015[32]	86	TheraSphere	TACE	Prospective comparative	Adults with intermediate-stage (BCLC B) unresectable HCC. Patients eligible for curative therapy were excluded
Salem 2013[33]	56	TheraSphere	TACE	Prospective comparative	No relevant outcomes were reported
Woodall 2009[37]	52	TheraSphere	BSC	Prospective comparative	Patients with advanced-stage HCC, ineligible for transplant
Memon 2014[83]	96	TheraSphere	TACE	Prospective comparative	No relevant outcomes reported
Maccauro 2014[36]	45	TheraSphere plus sorafenib	TheraSphere	Matched case–control study	Patients with intermediate/ advanced HCC with PVT, not appropriate for transplant
Salem 2011[47]	245	TheraSphere	TACE	Retrospective comparative	Majority of patients had early/ intermediate-stage HCC (88.1%) and 39% were within Milan transplant criteria (T2) but there were no relevant outcomes reported

continued

TABLE 7 Network 1: adults with unresectable HCC who are potentially eligible for transplant (*continued*)

Study (first author and year)	*n*	Intervention	Comparator	Study design	Reason for inclusion/exclusion
Bhangoo 2015[41]	17	TheraSphere	SIR-Spheres	Retrospective comparative	Patients with intermediate/advanced unresectable HCC who either failed or had disease not amenable to alternative locoregional therapies
Cho 2016[43]	63	SIR-Spheres	Sorafenib	Retrospective comparative	Patients with BCLC stage C HCC with PVT, not appropriate for transplant
de la Torre 2016[44]	73	SIR-Spheres	Sorafenib	Retrospective comparative	Patients with HCC with PVI, not appropriate for curative therapy
Van Der Gucht 2017[40]	77	SIR-Spheres	TheraSphere	Retrospective comparative	Patients with early, intermediate and advanced HCC, not appropriate for curative therapy
Biederman 2016[39]	90	SIR-Spheres	TheraSphere	Retrospective comparative	Patients with unresectable HCC with main or lobar PVT, not appropriate for curative therapy
Akinwande 2016[49,50]	96 (matched cohort of 358 patients)	TheraSphere	DEB-TACE	Retrospective comparative	Adults with unresectable HCC (with or without PVT), unlikely transplant intent
Soydal 2016[46]	80	SIR-Spheres	TACE	Retrospective comparative	Patients with intermediate/advanced-stage HCC, some patients with extrahepatic metastases
Gramenzi 2015[45]	137	SIR-Spheres	Sorafenib	Retrospective comparative	Patients with intermediate/advanced HCC, not appropriate for curative therapy
Moreno-Luna 2013[48]	116	TheraSphere	TACE	Retrospective comparative	Excluded patients eligible for curative therapy
Biederman 2015[38]	97	TheraSphere	SIR-Spheres	Retrospective comparative	Adults with advanced HCC with PVT, not eligible for curative therapy
d'Abadie 2018[42]	45	SIR-Spheres	TheraSphere	Retrospective comparative	Unclear population

Network 2: adults with unresectable hepatocellular carcinoma who are eligible for conventional transarterial therapies

The second model was for patients with unresectable HCC who are eligible for CTTs. Patients in this population tend to have intermediate-stage HCC (BCLC B); however, patients with advanced-stage HCC (BCLC C) can also be eligible if they do not have PVT/PVI or extrahepatic spread. Studies in which the majority of patients had intermediate-stage HCC (BCLC B) and $\leq$ 30% of patients had advanced disease (BCLC C) were included. If studies reported results split by disease stage, they were included. A small proportion of patients in this population may also be eligible for downstaging to transplant; however, there was very little evidence to inform this. Furthermore, clinicians advised that the role of downstaging HCC for liver transplantation is currently under evaluation in the UK and SIRT is not specifically required for downstaging as this can be achieved using existing therapies, most commonly TACE.

After screening the 39 studies described in the previous section, seven studies were identified as relevant for the population of patients who are eligible for CTT: six RCTs and one retrospective comparative study. The reasons for inclusion and exclusion are listed in *Table 8*. The main reason for exclusion was the population being substantially mixed in terms of stage of HCC disease or patients having advanced-stage disease, which made them ineligible for CTT. SIRTACE,[22] which is a RCT comparing SIR-Spheres and TACE described in *Chapter 3*, *Efficacy and safety of SIR-Spheres*, included a mixed population of patients with early-, intermediate- and advanced-stage HCC. The trial was funded by Sirtex; therefore, data split by disease stage were requested. However, Sirtex was unable to provide the data as it did not have access to them, so the trial could not be included in the NMA.

TABLE 8 Network 2: adults with unresectable HCC who are eligible for CTTs

Study (first author and year)	*n*	Intervention	Comparator	Study design	Reason for inclusion/exclusion
***Studies included in this network* (n = *7*)**					
Pitton 2015[23]	24	SIR-Spheres	DEB-TACE	RCT	Patients with intermediate-stage HCC (BCLC stage B)
Yu 2014[65]	98	TACE	TAE	RCT	Patients with unresectable HCC, Child–Pugh class A or B, ECOG < 2
Malagari 2010[66]	87	DEB-TACE	TAE	RCT	Patients unsuitable for curative treatments with potentially resectable lesions but at high risk for surgery
Sacco 2011[59]	67	DEB-TACE	TACE	RCT	Patients with untreated HCC, Child–Pugh class A or B, ECOG 0–1
Chang 1994[63]	46	TACE	TAE	RCT	Patients with inoperable HCC, Child–Pugh class A or B
Meyer 2013[64]	86	TACE	TAE	RCT	Patients with untreated, unresectable HCC, Child–Pugh class A or B, ECOG 0–2
Van Der Gucht 2017[40]	35 (subgroup of 77 patients)	SIR-Spheres	TheraSphere	Retrospective comparative	Subgroup of early/intermediate-HCC patients
***Studies excluded from this network* (n = *32*)**					
Kolligs 2015[22] (SIRTACE)	28	SIR-Spheres	TACE	RCT	Mixed population of early- and intermediate-stage patients, without portal vein occlusion. Pilot trial funded by Sirtex. Data for intermediate patients were requested but not provided
Vilgrain 2017[19,84] (SARAH)	459	SIR-Spheres	Sorafenib	RCT	Patients with locally advanced HCC or new HCC not eligible for surgery/ablation after previously cured HCC or HCC with two unsuccessful rounds of TACE. Poor candidates for TACE
Salem 2016[25] (PREMIERE)	45	TheraSphere	TACE	RCT	Patients with early/intermediate-HCC with no vascular invasion. The intent of therapy was bridge to transplant

continued

TABLE 8 Network 2: adults with unresectable HCC who are eligible for CTTs (*continued*)

Study (first author and year)	*n*	Intervention	Comparator	Study design	Reason for inclusion/exclusion
Kulik 2014[28]	20	TheraSphere	TheraSphere plus sorafenib	RCT	Intent of therapy was bridge to transplant
Chow 2018[21] (SIRveNIB)	360	SIR-Spheres	Sorafenib	RCT	Sorafenib is an irrelevant comparator in this population
Lammer 2010[56,57] (PRECISION)	212	DEB-TACE	TACE	RCT	No relevant outcomes reported
Ricke 2015[24] (SORAMIC)	40	SIR-Spheres plus sorafenib	Sorafenib	RCT	Poor candidates for TACE
van Malenstein 2011[60]	30	DEB-TACE	TACE	RCT	No relevant outcomes reported
Brown 2016[67]	101	DEB-TACE	TAE	RCT	Mixed population and some patients have PVI
Golfieri 2014[58]	177	DEB-TACE	TACE	RCT	Patients with early-, intermediate- and advanced-stage HCC without PVT. The population is too varied to include
Llovet 2002[61]	112	TACE	TAE	RCT	Patients with intermediate/advanced-stage HCC without PVI/extrahepatic disease but no relevant outcomes reported
Kawai 1992[62]	289	TACE	TAE	RCT	Patients with early/intermediate-stage HCC but no relevant outcomes reported
Kudo 2018[81] (REFLECT)	289 (subgroup of 954 patients)	Lenvatinib	Sorafenib	RCT	Subgroup of patients with advanced-stage HCC, majority had PVI or extrahepatic spread – ineligible for TACE
Llovet 2008[80] (SHARP)	602	Sorafenib	Placebo	RCT	Adults with intermediate/advanced-stage HCC, majority had extrahepatic spread/MVI. Patients ineligible for TACE
Hickey 2016[35]	765	TheraSphere	TACE	Prospective comparative	Adults with early-, intermediate- and advanced-stage HCC but significant baseline imbalances in age, PVI, number of lesions and CP class
Kirchner 2019[31]	94	TheraSphere	TACE/DEB-TACE	Prospective comparative	No relevant outcomes reported
Memon 2013[34]	96	TheraSphere	TACE	Prospective comparative	No relevant outcomes reported
Salem 2013[33]	56	TheraSphere	TACE	Prospective comparative	No relevant outcomes reported
El Fouly 2015[32]	86	TheraSphere	TACE	Prospective comparative	Patients with intermediate-stage HCC but systematic selection bias and baseline imbalances in age, tumour size and tumour number were detected
Woodall 2009[37]	52	TheraSphere	BSC	Prospective comparative	Patients with advanced-stage HCC, ineligible for TACE

TABLE 8 Network 2: adults with unresectable HCC who are eligible for CTTs (*continued*)

Study (first author and year)	*n*	Intervention	Comparator	Study design	Reason for inclusion/exclusion
Maccauro 2014[36]	45	TheraSphere plus sorafenib	TheraSphere	Matched case–control study	Patients with intermediate/ advanced HCC, poor candidates for TACE
Akinwande 2016[49]	96 (subgroup of 358 patients)	TheraSphere	DEB-TACE	Retrospective comparative	Mixed population of patients with unresectable HCC with or without PVT, results not split by disease stage
Bhangoo 2015[41]	17	TheraSphere	SIR-Spheres	Retrospective comparative	Patients ineligible for TACE (patients had either failed or were not amenable to other locoregional therapies)
Moreno-Luna 2013[48]	116	TheraSphere	TACE	Retrospective comparative	Patients with unresectable HCC not eligible for transplant but significant baseline imbalances between groups in ECOG status, Child–Pugh class, number of tumours and BCLC stage
Cho 2016[43]	63	SIR-Spheres	Sorafenib	Retrospective comparative	Patients ineligible for TACE
de la Torre 2016[44]	73	SIR-Spheres	Sorafenib	Retrospective comparative	Patients ineligible for TACE
Biederman 2016[39]	90	SIR-Spheres	TheraSphere	Retrospective comparative	Patients ineligible for TACE
Gramenzi 2015[45]	137	SIR-Spheres	Sorafenib	Retrospective comparative	Patients were ineligible or unsuitable for TACE
Biederman 2015[38]	97	SIR-Spheres	TheraSphere	Retrospective comparative	Patients with unresectable, advanced-stage HCC with PVT, poor candidates for TACE
d'Abadie 2018[42]	45	SIR-Spheres	TheraSphere	Retrospective comparative	Population unclear. Appears to include both patients eligible and non-eligible for TACE
Salem 2011[47]	245	TheraSphere	TACE	Retrospective comparative	Mixed population of patients with HCC without PVT or extrahepatic metastases but results not stratified by BCLC stage
Soydal 2016[46]	80	TACE	SIR-Spheres	Retrospective comparative	Patients with intermediate/ advanced-stage HCC, some patients with extrahepatic metastases

The studies included in network 2 were a RCT directly comparing SIR-Spheres with DEB-TACE,[23] five RCTs comparing different CTTs[59,63–66] and one retrospective comparative study comparing SIR-Spheres with TheraSphere.[40] The RCT that compared SIR-Spheres with DEB-TACE[23] included only 24 patients (described in more detail in *Chapter 3*, *Efficacy and safety of SIR-Spheres*) and was the only direct evidence between SIR-Spheres and CTT. There were no studies comparing TheraSphere with CTT. The retrospective study comparing SIR-Spheres with TheraSphere[40] was rated as being at a high risk of bias, as described in *Chapter 3*, *Efficacy and safety of SIR-Spheres*.

The five RCTs comparing different CTTs, which were deemed relevant for this population, were included to inform the network. This includes three RCTs comparing TACE and TAE.[63–65] The risk-of-bias assessment reported some concerns regarding bias in the randomisation process for all three trials. The assessment also highlighted concerns regarding protocol deviations from the intended interventions for Chang *et al.*[63] Both Yu *et al.*[65] and Meyer *et al.*[64] showed no significant differences in OS or PFS. Chang *et al.*[63] reported only survival rates between groups but did not find any significant differences.

There was one RCT comparing DEB-TACE and TAE: Malagari *et al.*[66] The risk-of-bias assessment reported some concerns with this study regarding bias in the randomisation process and in protocol deviations from the intended interventions. The trial was conducted in 95 patients and found that TTP was significantly longer in the DEB-TACE arm (42.4 ± 9.5 weeks) than in the TAE arm (36.2 ± 9.0 weeks). The remaining RCT compared DEB-TACE and TACE: Sacco *et al.*[59] This trial was rated as being at a high overall risk of bias owing to an open randomisation process. The trial found no significant differences in survival rates or other relevant outcomes between the two groups. Full results of the risk-of-bias judgements are presented in *Appendix 9* and the study details and results are presented in *Appendix 10*.

The network diagram representing the model is shown in *Figure 2*. There are missing direct comparisons and there is no common comparator in the evidence base for both OS and PFS outcomes in this population; therefore, it forms a 'disconnected network'. Implementing a NMA in this population would produce very uncertain results as it relies on a single small trial by Pitton *et al.*[23] to connect SIR-Spheres in the network. Furthermore, it would not provide reliable evidence on TheraSphere comparisons with CTT as there is only one small, retrospective, low-quality study connecting TheraSphere in the network. Therefore, network 2, of patients with unresectable HCC who are eligible for CTT, was not conducted as it was deemed unsuitable for decision-making.

Network 3: adults with unresectable hepatocellular carcinoma who are ineligible for conventional transarterial therapies

The third model was for patients with unresectable HCC who are ineligible for CTT. Patients in this population tend to have advanced-stage HCC (BCLC C) with or without PVT/PVI. This population may, however, include some patients with intermediate-stage disease (BCLC B) who are ineligible for CTT or who have previously failed CTT.

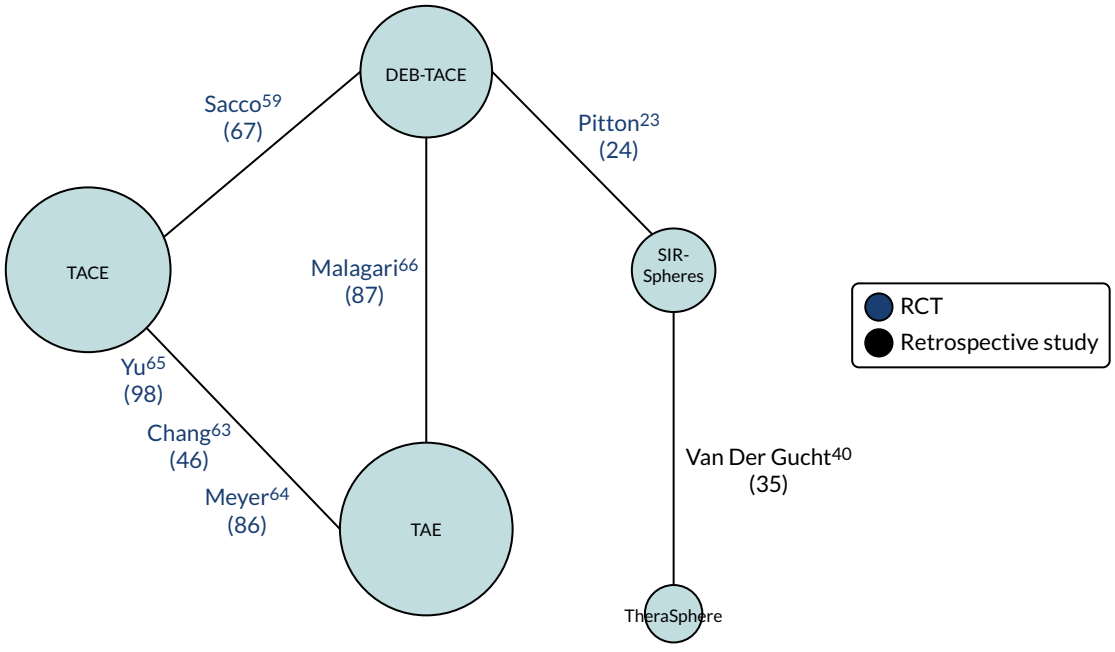

FIGURE 2 Network 2: patients eligible for CTTs.

There were 26 comparative studies included in the systematic review of clinical effectiveness, which were identified as potentially eligible for the third network; the 11 RCTs comparing different CTTs were not screened as they are not relevant for this population. A further two studies of systemic therapies identified from previous technology appraisals were additionally screened for inclusion in this network. Out of 28 studies, three RCTs and five retrospective comparative studies were initially selected as relevant for this population. Twenty studies were excluded, mainly because of irrelevant comparisons or not reporting relevant outcomes. The NMA diagram is illustrated in *Figure 3*.

The network includes robust direct evidence between SIR-Spheres and sorafenib from the two large RCTs SARAH[84] and SIRveNIB,[21] which are described in more detail in *Chapter 3*, *Efficacy and safety of SIR-Spheres*. There are also three smaller retrospective comparative studies comparing SIR-Spheres and sorafenib.[44,45,85] On closer examination, all three of these studies were rated as being at a high risk of bias owing to an imbalance in baseline characteristics, unclear reporting of missing data and unblinded outcome assessors (see *Appendix 8*). Therefore, owing to already having identified high-quality RCTs comparing SIR-Spheres and sorafenib, these three retrospective studies were removed. Including low-quality studies where there is already reliable evidence may invalidate the NMA and consequently the results. Furthermore, the two retrospective studies, Biederman *et al.*[39] and Van Der Gucht *et al.*,[40] were also considered to have a high risk of bias, as described in *Chapter 3*, *Direct comparisons of different selective internal radiation therapies*. However, these studies were included as a sensitivity analysis as they are the only studies with direct evidence between TheraSphere and SIR-Spheres.

The network was updated and the final NMA of patients ineligible for CTT includes two RCTs comparing SIR-Spheres and sorafenib,[19,21] one RCT comparing lenvatinib and sorafenib[81] and two retrospective comparative studies comparing SIR-Spheres and TheraSphere (included as a sensitivity analysis) (*Figure 4*).[38,40] The decisions for including and excluding each study are detailed in *Table 9*. The study selection process for this NMA (updated network 3) is illustrated in *Figure 5*.

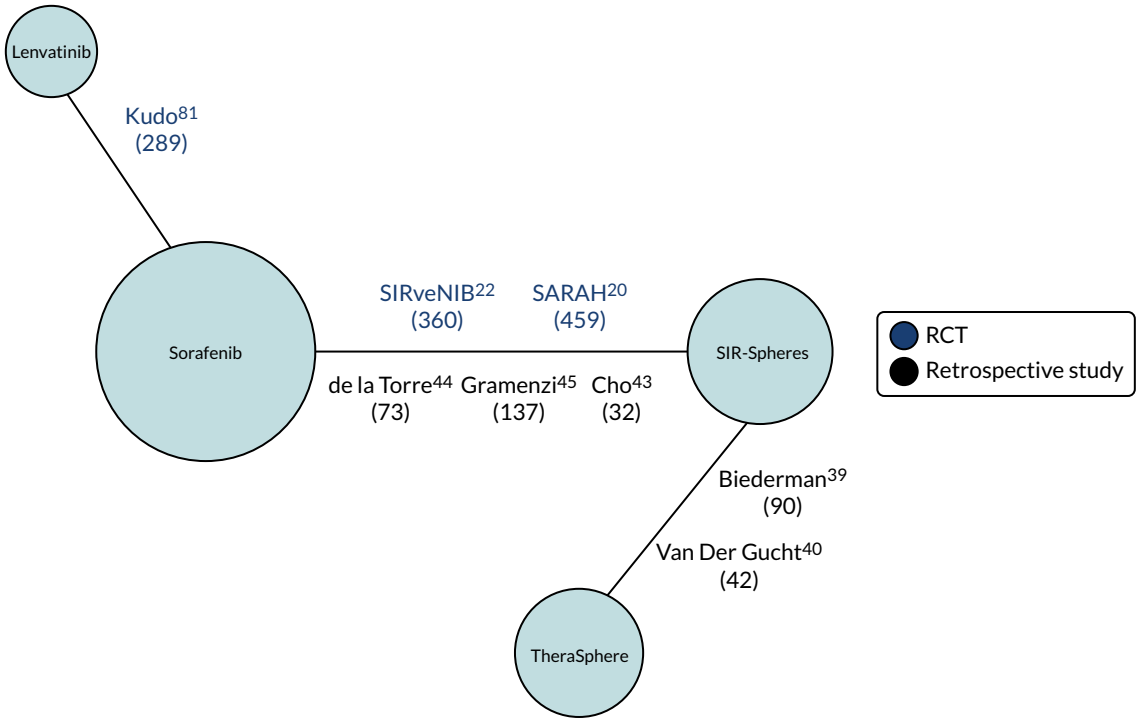

FIGURE 3 Network 3: adults with unresectable HCC who are ineligible for CTTs.

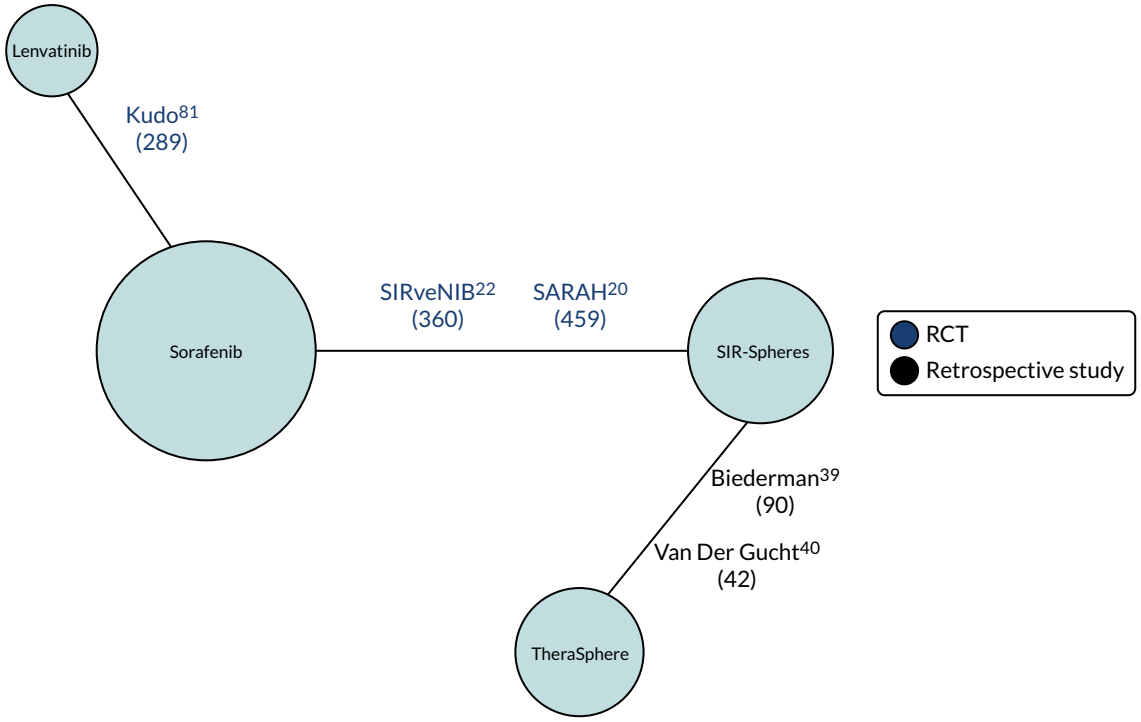

FIGURE 4 Updated network 3: adults with unresectable HCC who are ineligible for CTTs.

TABLE 9 Network 3: adults with unresectable HCC who are ineligible for CTTs

Study (first author and year)	*n*	Intervention	Comparator	Study design	Reason for inclusion/exclusion
Studies included in this network **(n = *5*)**					
Chow 2018[21] (SIRveNIB)	360	SIR-Spheres	Sorafenib	RCT	Patients with locally advanced HCC
Vilgrain 2017[19,84] (SARAH)	459	SIR-Spheres	Sorafenib	RCT	Adults with locally advanced HCC (BCLC C) or new HCC not eligible for surgery/ablation after previously cured HCC or HCC with two unsuccessful rounds of TACE
Kudo 2018[81] (REFLECT)	289 (subgroup of 954 patients)	Lenvatinib	Sorafenib	RCT	Subgroup of adults with advanced-stage HCC, majority had PVI or extrahepatic spread
Van Der Gucht 2017[40]	42 (subgroup of 77 patients)	SIR-Spheres	TheraSphere	Retrospective comparative	Subgroup of advanced-stage HCC patients
Biederman 2016[39]	90	SIR-Spheres	TheraSphere	Retrospective comparative	Patients with unresectable HCC and main or lobar PVT
Studies excluded from this network **(n = *23*)**					
Ricke 2015[24] (SORAMIC)	40	SIR-Spheres plus sorafenib	Sorafenib	RCT	Adults with unresectable intermediate or advanced HCC, poor candidate for TACE. Only safety analyses are published. Data were requested from company but, as this is an investigator-initiated trial, the data were not available

TABLE 9 Network 3: adults with unresectable HCC who are ineligible for CTTs (*continued*)

Study (first author and year)	*n*	Intervention	Comparator	Study design	Reason for inclusion/exclusion
Llovet 2008[80] (SHARP)	602	Sorafenib	Placebo	RCT	Adults with intermediate/ advanced-stage HCC, majority had extrahepatic spread/ vascular invasion. This study was not required for the NMA as it did not provide any extra information and was not needed for the cost-effectiveness model
Salem 2016[25] (PREMIERE)	45	TheraSphere	TACE	RCT	Compared TACE – irrelevant comparison in this population
Kolligs 2015[22] (SIRTACE)	28	SIR-Spheres	TACE	RCT	Compared TACE – irrelevant comparison in this population
Pitton 2015[23]	24	SIR-Spheres	DEB-TACE	RCT	Compared DEB-TACE – irrelevant comparison in this population
Kulik 2014[28]	20	TheraSphere	TheraSphere plus sorafenib	RCT	Mixed population with the intent to bridge to transplant
Kirchner 2019[31]	94	TheraSphere	TACE/ DEB-TACE	Prospective comparative	Compared TACE – irrelevant comparison in this population
Hickey 2016[35]	765	TheraSphere	TACE	Prospective comparative	Compared TACE – irrelevant comparison in this population
El Fouly 2015[32]	86	TheraSphere	TACE	Prospective comparative	Compared TACE – irrelevant comparison in this population
Woodall 2009[37]	52	TheraSphere	BSC	Prospective comparative	Patients with advanced-stage HCC. Excluded owing to systematic selection bias and significant baseline imbalances
Memon 2013[34]	96	TheraSphere	TACE	Prospective comparative	No relevant outcomes reported
Salem 2013[33]	56	TheraSphere	TACE	Prospective comparative	No relevant outcomes reported and compared TACE – irrelevant comparison in this population
Maccauro 2014[36]	45	TheraSphere plus sorafenib	TheraSphere	Matched case–control study	Patients with intermediate/ advanced-stage HCC. No relevant outcomes reported
Cho 2016[43]	63	SIR-Spheres	Sorafenib	Retrospective comparative	Patients with BCLC stage C HCC and PVI. However, study of low quality and high risk of bias, and therefore excluded from updated network
de la Torre 2016[44]	73	SIR-Spheres	Sorafenib	Retrospective comparative	Patients with unresectable HCC and PVI. However, study of low quality and high risk of bias and therefore excluded from updated network
Gramenzi 2015[45]	137	SIR-Spheres	Sorafenib	Retrospective comparative	Patients with intermediate/ advanced-stage HCC unfit for other effective therapies. However, study of low quality and high risk of bias, and therefore excluded from updated network

continued

TABLE 9 Network 3: adults with unresectable HCC who are ineligible for CTTs (*continued*)

Study (first author and year)	*n*	Intervention	Comparator	Study design	Reason for inclusion/exclusion
Akinwande 2016[49]	96	TheraSphere	DEB-TACE	Retrospective comparative	Compared TACE – irrelevant comparison in this population
Moreno-Luna 2013[48]	116	TheraSphere	TACE	Retrospective comparative	Compared TACE – irrelevant comparison in this population
Salem 2011[47]	245	TheraSphere	TACE	Retrospective comparative	Compared TACE – irrelevant comparison in this population
d'Abadie 2018[42]	45	SIR-Spheres	TheraSphere	Retrospective comparative	Population unclear. Appears to include patients both eligible and non-eligible for TACE
Bhangoo 2015[41]	17	TheraSphere	SIR-Spheres	Retrospective comparative	Mixed population of patients with unresectable HCC, who had either failed or were not amenable to other locoregional therapies. No relevant outcomes reported
Biederman 2015[38]	97	SIR-Spheres	TheraSphere	Retrospective comparative	Adults with unresectable HCC with PVT. No relevant outcomes reported
Soydal 2016[46]	80	TACE	SIR-Spheres	Retrospective comparative	Compared TACE – irrelevant comparison

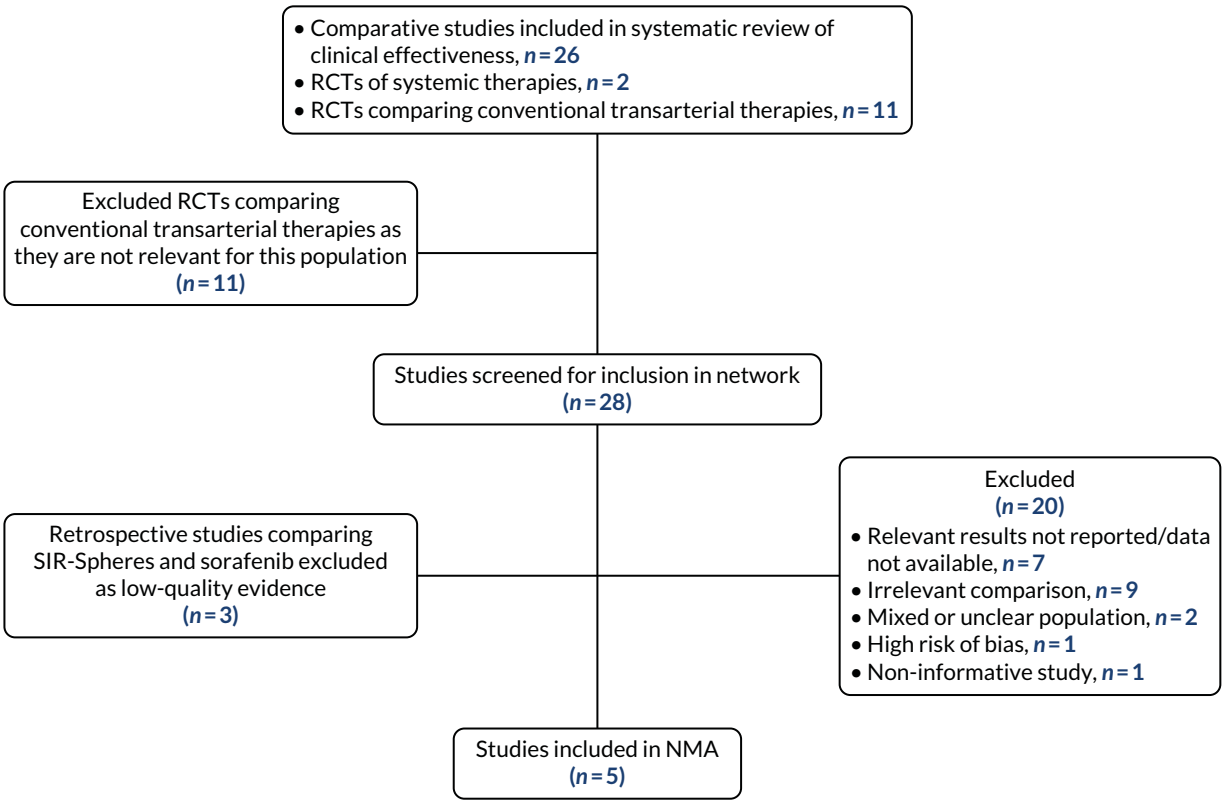

FIGURE 5 Flow diagram of the study selection process for the NMA of adults ineligible for CTTs.

Methods of data analysis

This section describes a NMA of all relevant RCTs (*Table 10*) and a NMA of RCTs that included only patients with Child–Pugh class A liver function. Currently, in the UK, systemic therapy, such as sorafenib and lenvatinib, is licensed for only Child–Pugh class A patients with unresectable HCC. However, results for all patients in the ITT population are reported in *Appendix 12*, *Tables 39* and *40*.

In the SARAH[19] and SIRveNIB[21] trials, 22.4% and 28.6% of patients allocated to SIR-Spheres did not receive SIRT. Patients who did not receive their allocated treatment were excluded from the per-protocol analysis. Therefore, the NMA of Child–Pugh class A patients with unresectable HCC who are ineligible for CTT in the per-protocol population is the base-case scenario. However, the ITT results are used for the REFLECT trial.[12] Therefore, the results for the ITT population are also reported. Both OS and PFS were assessed as outcomes. However, PFS in Child–Pugh class A patients was not reported for the SIRveNIB study[21] or for patients in the Biederman *et al.*[39] study. Therefore, PFS could not be assessed in the base-case population or in the sensitivity analyses.

The NMA was estimated using Bayesian Markov chain Monte Carlo techniques in WinBUGS, using code obtained from the NICE Decision Support Unit (DSU)'s Technical Support Document.[86] An initial burn-in of at least 50,000 simulations was used, and convergence was confirmed through visual inspection of the Brook–Gelman–Rubin diagnostic and history plots. This was followed by 100,000 simulations on three chains to estimate the sampled parameters. Where available, Kaplan–Meier (KM) data were extracted using methods reported by Guyot *et al.*[87] When KM data were not available, HRs and their variance were extracted, and log-hazard ratios synthesised. To synthesise HRs across studies, it is required that the proportional hazards assumption holds. Therefore, the deviation from proportional hazards was tested and the Schoenfeld residuals, survival curves and piecewise hazards visually inspected. It was decided to conduct more complex time-varying models only if simple models

TABLE 10 Summary of studies included in the NMA

Study (first author and year)	Treatment	*n*	Median age (years)	Male, *n* (%)	PVT/PVI, *n* (%)	BCLC classification, *n* (%)		
						A	B	C
Vilgrain 2017[19] (SARAH)	SIR-Spheres	174	66.3 ± 9.4	158 (90.8)	29 (16.7)[a]	7 (4.0)	53 (30.5)	114 (65.5)
	Sorafenib	206	64.6 ± 9.5	186 (90.3)	37 (18.0)[a]	9 (4.4)	54 (26.2)	143 (69.4)
Chow 2018[21] (SIRveNIB)	SIR-Spheres	130	60.9 (SD 11.5)	107 (82.3)	30 (23.1)[b]	0 (0)	79 (60.8)	50 (38.5)
	Sorafenib	162	57.5 (SD 10.6)	138 (85.2)	48 (29.6)[b]	1 (0.6)	88 (54.3)	73 (45.1)
NICE 2018[12] (REFLECT)[c]	Lenvatinib	369	–	–	0 (0)	–	–	–
	Sorafenib	386	–	–	0 (0)	–	–	–
Retrospective comparative studies								
Biederman 2016[39]	SIR-Spheres	21	60 ± 11.5	20 (95.2)	100%[d]	–	–	–
	TheraSphere	69	65.6 ± 11.3	54 (78.3)	100%[d]	–	–	–
[e]Van Der Gucht 2017[40]	SIR-Spheres	24	–	–	–	0 (0)	0 (0)	24 (100)
	TheraSphere	18	–	–	–	0 (0)	0 (0)	18 (100)

SD, standard deviation.
a Main PVI.
b PVT.
c Subgroup of patients with no extrahepatic spread or macroscopic PVI.
d Main and lobar PVT.
e Subgroup of patients with advanced-stage HCC.

were not a good fit to the data. A model was chosen by visually inspecting the development of the hazard over time for the different trials and then by comparing deviance information criterion (DIC) values for the competing models. It was decided that a hierarchical model with classes of treatments composed of individual treatments, which would allow each treatment effect to be estimated as well as the overall class mean, was not possible owing to the small number of studies in the NMA.[86] Finally, both fixed- and random-effects models were evaluated and between-trial heterogeneity was assessed using the between-study standard deviation (SD). Inconsistency did not need to be examined, as there were no loops in the network.

Model selection

A Bayesian evidence synthesis approach was employed. With a Bayesian framework, prior belief about a treatment effect is combined with a likelihood distribution that summarises the data to obtain a posterior distribution reflecting the belief about the treatment effect after incorporating the evidence. Normal identity link models were used for this NMA.[86] The Schoenfeld residuals were visually inspected and statistically tested for each survival curve except for the REFLECT study because only a subgroup of the data were used, for which there was no KM curve (see *Appendix 11*). Although the KM curves for each study cross over, which suggests that there are some concerns about the proportional hazards assumption, there is no clear statistical evidence that the assumption is violated for all of the included studies.[12] The viability of the network depends on the proportional hazards assumption. Therefore, HRs were synthesised across studies. The choice of prior distributions for the between-study variance was explored. A half-normal (0, 0.19^2) prior was chosen as a uniform (0, 3) prior was too influential. The justification for the half-normal prior is that it expresses the prior belief that 95% of trials will give HRs within a factor of 2 from the estimated median HR. However, owing to the small number of studies, there was little evidence to inform the between-study heterogeneity. The half-normal prior was also influential, although less so than the uniform prior. According to DIC and total residual deviance statistics, the fixed-effects model provided a better fit to the data than did the random-effects counterpart. The fixed-effects model had both a lower DIC and fewer parameters. This is again because of the small number of studies and the influence of the prior on the between-study heterogeneity. Owing to both models having similar results, the fixed-effects model was chosen as it is a simpler model. Results from both are presented for comparison.

Scenario and subgroup analyses

Scenario analyses including the two low-quality retrospective studies, by Biederman *et al.*[39] and Van Der Gucht *et al.*,[40] were carried out, as discussed in *Chapter 3*, *Network 3: adults with unresectable hepatocellular carcinoma who are ineligible for conventional transarterial therapies*. For the first scenario, the Biederman *et al.*[39] study was added to the base-case NMA: adults with unresectable HCC who are Child–Pugh class A and ineligible for CTT in both the per-protocol population and the ITT population. There were no available data on Child–Pugh class A patients in the Van Der Gucht *et al.*[40] study; therefore, it was not included. For the second scenario, which is reported in *Appendix 12*, both the Biederman *et al.*[39] and Van Der Gucht *et al.*[40] studies were added to the NMA of all adults who are ineligible for CTT in the ITT population. Biederman *et al.*[39] did not report PFS outcomes; therefore, the second scenario was used for the OS outcome only.

A sensitivity analysis that excluded the RCT SIRveNIB[21] was conducted. Patients in the SIRveNIB trial are from the Asia-Pacific region and, thus, have different HCC disease aetiology and consequently differing treatments to those from Europe. This is discussed in more detail in *Chapter 3*, *Efficacy and safety of SIR-Spheres*. Therefore, a scenario was conducted in which SIRveNIB was excluded from the base-case NMA.

It was not possible to conduct a subgroup analysis in Child–Pugh class A patients with PVT or in patients with PVI. The only available data for this subgroup of patients were from the two RCTs comparing SIR-Spheres and sorafenib: SARAH[19,20] and SIRveNIB.[21] However, SIRveNIB reported results for only the subgroup of patients with PVT, and SARAH reported results for only patients with PVI.

Results

Results of the base-case network meta-analysis in the per-protocol population: adults with unresectable hepatocellular carcinoma who are Child–Pugh class A and ineligible for conventional transarterial therapy

Three studies were included in the base-case analysis: two RCTs comparing SIR-Spheres and sorafenib and one RCT comparing lenvatinib and sorafenib. The baseline characteristics of these studies are detailed in *Table 10*. The REFLECT trial,[81] which compares lenvatinib and sorafenib, included patients with extrahepatic spread (61% in the lenvatinib arm and 62% in the sorafenib arm). All the other trials excluded patients with extrahepatic spread; therefore, the subgroup of patients without extrahepatic spread or PVI was used for the REFLECT trial. A more appropriate subgroup was not reported.

The results of both the fixed-effects analysis and the random-effects analysis are shown in *Table 11*.

The results provide no evidence that the random-effects model should be preferred. The DIC is marginally higher (–0.40 for the random-effects model, compared with –1.38 for the fixed-effects model; lower DIC values are preferred, with differences of 2–5 considered important).[86] In addition, the high level of uncertainty around the random-effects CrI indicates that there is little information to inform the random-effects parameter. Therefore, the results of the fixed-effects model will be used for the base-case and all scenario analyses. Both fixed-effects and random-effects results are reported in *Appendix 13*, *Tables 43–46*, for comparison.

There were no meaningful differences in OS in the per-protocol population between any of the three treatments and all treatments appear to have a similar effect. SIR-Spheres shows a marginal improvement in OS when compared with sorafenib (HR 0.94, 95% CrI 0.77 to 1.14) and lenvatinib (HR 0.91, 95% CrI 0.63 to 1.26); however, the treatment effects are uncertain as the CrI crosses 1. Lenvatinib shows a marginal reduction in OS when compared with sorafenib (HR 1.06, 95% CrI 0.79 to 1.40), although again the CrI crosses 1 (*Table 12*). *Figure 6* presents the cumulative ranking curves for each treatment, with rank 1 being the best and rank 3 being the worst. SIR-Spheres was ranked as the most efficacious therapy, with a

TABLE 11 Overall survival results for the base-case NMA in the per-protocol population

		HR (95% CrI)	
Intervention	**Comparator**	**Fixed effects**	**Random effects**
SIR-Spheres	Sorafenib	0.94 (0.77 to 1.14)	0.94 (0.68 to 1.26)
SIR-Spheres	Lenvatinib	0.91 (0.63 to 1.26)	0.92 (0.52 to 1.51)
Lenvatinib	Sorafenib	1.06 (0.79 to 1.40)	1.08 (0.68 to 1.64)
SD		–	0.13 (0.005 to 0.380)
DIC		–1.38	0.40
pD		2.0	2.5

pD, number of parameters.

TABLE 12 Hazard ratio estimates (95% CrIs) for OS for each treatment comparison for the base-case NMA in the per-protocol population

Sorafenib	1.07 (0.88 to 1.29)	0.96 (0.72 to 1.27)
0.94 (0.77 to 1.14)	SIR-Spheres	0.91 (0.63 to 1.26)
1.06 (0.79 to 1.40)	1.14 (0.79 to 1.58)	Lenvatinib

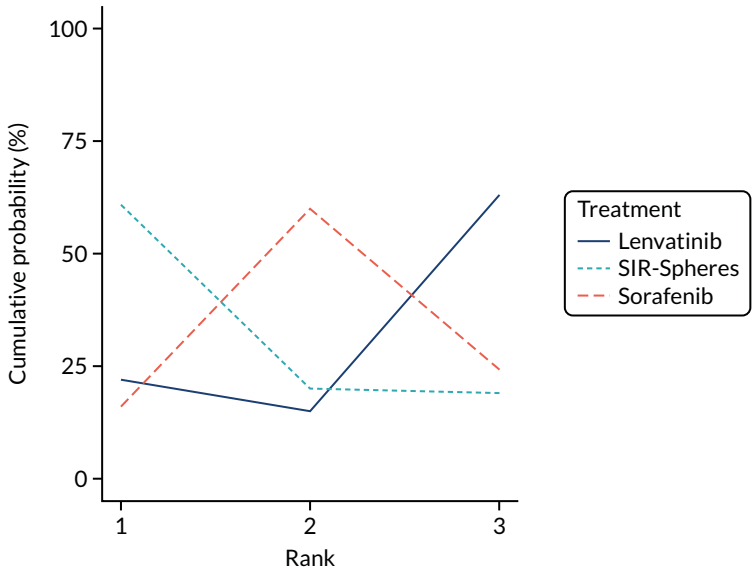

FIGURE 6 Cumulative ranking probability plots for each treatment in the base-case NMA for the per-protocol population.

probability of being the best of 0.61. Lenvatinib was ranked as the worst treatment, with a probability of being best of 0.22. Sorafenib was ranked as the second best, with a probability of being best of 0.16.

Results of the base-case network meta-analysis in the intention-to-treat population: adults with unresectable hepatocellular carcinoma who are Child–Pugh class A and ineligible for conventional transarterial therapy

Similar to the per-protocol population, there were no significant differences between treatments in the base-case NMA in the ITT population (*Table 13*).

SIR-Spheres appears to increase mortality when compared with sorafenib and lenvatinib (HR 1.13, 95% CrI 0.96 to 1.32 and 1.09, 95% CrI 0.77 to 1.48, respectively). However, the CrIs indicate that these results are uncertain. Lenvatinib also shows a reduction in OS when compared with sorafenib (1.06, 95% CrI 0.79 to 1.40); however, the 95% CrI crosses 1, indicating that there is not a significant treatment effect.

The HRs for all patients in the ITT population for OS and PFS are shown in *Appendix 12*, *Tables 41* and *42*, respectively.

TABLE 13 Overall survival results for the base-case NMA in the ITT population

		HR (95% CrI)	
Intervention	**Comparator**	**Fixed effects**	**Random effects**
SIR-Spheres	Sorafenib	1.13 (0.96 to 1.32)	1.13 (0.86 to 1.47)
SIR-Spheres	Lenvatinib	1.09 (0.77 to 1.48)	1.10 (0.66 to 1.74)
Lenvatinib	Sorafenib	1.06 (0.79 to 1.40)	1.07 (0.70 to 1.59)
SD		–	0.11 (0.004 to 0.352)
DIC		−3.04	−0.86
pD		2.00	2.00

pD, number of parameters.

Scenario 1: inclusion of Biederman *et al.* into the base-case network meta-analysis

The Biederman *et al.*[39] study was added to the base-case NMA in a scenario analysis, which allowed for a comparison to be made against TheraSphere. Biederman *et al.*[39] reports a very strong treatment effect on OS with TheraSphere compared with SIR-Spheres (HR 0.40, 95% CrI 0.20 to 0.78). However, as discussed earlier, Biederman *et al.*[39] is a retrospective, poor-quality study; therefore, these results may either in part or in full reflect the impact of bias. Furthermore, all patients in the Biederman *et al.*[39] study have PVT, which is much higher than the proportion of patients who have PVT/PVI in the other included studies. Adding this study has a substantial effect on the NMA results. In the per-protocol population, TheraSphere shows a substantial significant improvement in OS when compared with SIR-Spheres (HR 0.44, 95% CrI 0.20 to 0.84), sorafenib (HR 0.41, 95% CrI 0.20 to 0.77) and lenvatinib (HR 0.40, 95% CrI 0.18 to 0.78). There were no significant differences in OS between any of the other treatments (*Table 14*).

Similarly, in the ITT population, there was a significant improvement in OS with TheraSphere compared with sorafenib (HR 0.47, 95% CrI 0.21 to 0.88), SIR-Spheres (HR 0.41, 95% CrI 0.20 to 0.77) and lenvatinib (HR 0.45, 95% CrI 0.20 to 0.89). There were no significant differences in OS between SIR-Spheres, sorafenib and lenvatinib (see *Table 14*).

Sensitivity analysis

Exclusion of the SIRveNIB study from the base-case network meta-analysis

The SIRveNIB trial,[21] which compares SIR-Spheres and sorafenib, was conducted in the Asia-Pacific region. This has implications for the generalisability of the SIRveNIB trial results to the UK population. The aetiology of HCC and the consequent treatment in the Asia-Pacific region are different, as described in more detail in *Chapter 3*, *Efficacy and safety of SIR-Spheres*. A sensitivity analysis was therefore implemented, in which the SIRveNIB study was excluded from the base-case NMA. Excluding SIRveNIB had very little impact on the results for OS in the ITT population compared with the base-case NMA. All treatment effects for all comparisons were similar to the base-case NMA (*Table 15*). The OS results in the per-protocol population, however, showed a slight change after excluding SIRveNIB. The treatment effect estimate for SIR-Spheres versus sorafenib increased (1.02, 95% CrI 0.79 to 1.29) compared with the base-case NMA (0.94, 95% CrI 0.77 to 1.14). This showed a reduction in OS with SIR-Spheres rather than an improvement, as seen in the base-case per-protocol population, although neither were statistically significant.

TABLE 14 Overall survival results adding Biederman *et al.* to the base-case NMA

		HR (95% CrI) (fixed effects)	
Intervention	**Comparator**	**Per-protocol population**	**ITT population**
SIR-Spheres	Sorafenib	0.94 (0.77 to 1.13)	1.13 (0.96 to 1.32)
SIR-Spheres	Lenvatinib	0.91 (0.63 to 1.26)	1.09 (0.77 to 1.48)
TheraSphere	SIR-Spheres	0.44 (0.20 to 0.84)	0.41 (0.20 to 0.77)
TheraSphere	Sorafenib	0.41 (0.20 to 0.77)	0.47 (0.21 to 0.88)
TheraSphere	Lenvatinib	0.40 (0.18 to 0.78)	0.45 (0.20 to 0.89)
Lenvatinib	Sorafenib	1.06 (0.79 to 1.40)	1.06 (0.79 to 1.40)
DIC		0.30	−1.32
pD		3.00	3.00

pD, number of parameters.

TABLE 15 Results of the base-case NMA excluding the SIRveNIB study

		OS HR (95% CrI)	
Intervention	Comparator	ITT population	Per-protocol population
SIR-Spheres	Sorafenib	1.14 (0.90 to 1.41)	1.02 (0.79 to 1.29)
SIR-Spheres	Lenvatinib	1.09 (0.75 to 1.55)	0.98 (0.66 to 1.40)
Lenvatinib	Sorafenib	1.06 (0.79 to 1.40)	1.06 (0.79 to 1.40)
DIC		–0.52	–0.34
pD		2.0	2.0

pD, number of parameters.

Summary of findings of relative efficacy from network meta-analysis

Treatment options and outcomes vary greatly for patients with unresectable HCC according to the severity of cancer and liver disease. Therefore, three NMA models were produced to represent the different populations of unresectable HCC patients: patients eligible for transplant, patients ineligible for transplant but eligible for CTT and patients ineligible for CTT.

The NMA in patients eligible for transplant was not conducted. Clinical advice was that there are short transplant waiting times in the UK, whereas these were much longer in the trials in the NMA. Therefore, the network may not be generalisable to the UK and there may be limited opportunity for benefit, given the short waiting times. Furthermore, the two RCTs included in the network have very small sample sizes and, therefore, any efficacy estimates produced would be highly uncertain. The NMA of patients eligible for CTT was also not conducted because of the lack of good-quality evidence in this population. There was only one RCT of 24 patients directly comparing SIR-Spheres and the comparator therapies of interest. There were no studies comparing TheraSphere and CTT. Therefore, with missing direct comparisons and only one small study to connect the network, results produced would be very uncertain and unsuitable for decision-making.

Several NMAs of patients who are ineligible for CTT were conducted for both OS outcomes and PFS outcomes in the per-protocol and ITT populations.

The base-case NMA was in adults with unresectable HCC who have Child–Pugh class A liver disease and are ineligible for CTT in the per-protocol population. Three studies were included in the base-case analysis: two RCTs comparing SIR-Spheres and sorafenib and one RCT comparing lenvatinib and sorafenib. The results provided no evidence that the random-effects model should be preferred. In addition, the high level of uncertainty around the random-effects CrI indicated that there is little information to inform the random-effect parameter. Therefore, the results of the fixed-effects model were used for the base-case and scenario analyses.

There were no meaningful differences in OS between any of the three treatments in the per-protocol or ITT populations. All treatments appear to have a similar effect. In the per-protocol population, SIR-Spheres showed a non-significant marginal improvement in OS when compared with sorafenib (HR 0.94, 95% CrI 0.77 to 1.14), although the CrI indicates that this result is uncertain. SIR-Spheres was ranked as the most efficacious therapy, with a probability of being the best of 0.61. Lenvatinib was ranked as the worst treatment, with a probability of being best of 0.22. Sorafenib was ranked as the second best, with a probability of being best of 0.16.

To produce an efficacy estimate for TheraSphere, the only two studies that directly compared TheraSphere and SIR-Spheres for patients ineligible for CTT, Biederman *et al.*[39] and Van Der Gucht *et al.*,[40] were included as a sensitivity analysis. Both are low-quality retrospective studies, which reported strong treatment effects

on OS with TheraSphere compared with SIR-Spheres (HR 0.40, 95% CrI 0.20 to 0.78, and HR 0.77, 95% CrI 0.27 to 2.18, respectively). Adding these studies had a substantial effect on the NMA results. In the per-protocol population, TheraSphere showed a substantial and statistically significant improvement in OS when compared with SIR-Spheres (HR 0.44, 95% CrI 0.20 to 0.84), sorafenib (HR 0.41, 95% CrI 0.20 to 0.77) and lenvatinib (HR 0.40, 95% CrI 0.18 to 0.78). In the ITT population, there was also a significant improvement in OS with TheraSphere when compared with sorafenib (HR 0.53, 95% CrI 0.31 to 0.84), SIR-Spheres (HR 0.46, 95% CrI 0.28 to 0.72) and lenvatinib (HR 0.51, 95% CrI 0.28 to 0.86). A sensitivity analysis, which excluded the SIRveNIB study from the base-case NMA was also conducted. The SIRveNIB trial, which compared SIR-Spheres and sorafenib, was conducted in the Asia-Pacific region. This has implications for the generalisability of the SIRveNIB trial results to the UK population. Excluding SIRveNIB, however, had very little impact on the results for OS and PFS in the per-protocol and ITT populations compared with the base-case NMA. There were no significant differences in treatment effects for any comparisons.

Chapter 5 Assessment of existing cost-effectiveness evidence

Systematic review of existing cost-effectiveness evidence

This section presents a systematic review of previous economic evaluations of SIRT and provides an overview of these assessments and a discussion of their relevance to the UK NHS. The findings from the review were used to help inform the development of a new decision-analytic model, which is reported in *Chapter 7*.

Methods

Systematic searches for relevant literature were completed as part of the search used to identify clinical effectiveness studies. These searches included a broad set of terms aimed at identifying any evidence relating to SIRT, including studies evaluating the cost-effectiveness of SIRT. Details of the searches undertaken are reported in *Chapter 3*, *Search strategy*, and the full search strategy is reported in *Appendix 1*.

Study selection was conducted in two stages: (1) titles and abstracts identified by the search strategy were examined and screened as part of the clinical effectiveness review for any study potentially relevant to the cost-effectiveness review, and (2) full texts were then obtained and screened for inclusion. Screening of titles and abstracts, therefore, aligned with the selection approach outlined in *Chapter 3*, *Search strategy*; a single reviewer screened all studies, with 10% checked by a second reviewer. Full-text screening was conducted independently by two reviewers, with disagreements resolved by consensus. All studies meeting the inclusion criteria were summarised and used to identify potential structural issues, assumptions and key drivers of cost-effectiveness. The quality of the cost-effectiveness studies was assessed using a modified version of the Philips checklist[88] (see *Appendix 14*, *Table 47*).

Studies were included in the review if they assessed the cost-effectiveness of a SIRT versus any other therapy in a HCC population. A broad range of studies were considered for inclusion in the review, including economic evaluations conducted alongside trials, modelling studies and analyses of administrative databases. Only full economic evaluations comparing two or more options including both costs and consequences (cost-effectiveness, cost–utility or cost–benefit analyses) were included.

Results of the review of existing cost-effectiveness evidence

As described in *Chapter 3*, *Quantity and quality of research available*, a total of 34 records were identified as being potentially relevant to cost-effectiveness. The full-text articles of these records were assessed for eligibility, with a total of seven studies (eight publications) found to meet the inclusion criteria. Three studies were reported as full papers and four were reported as abstracts only. A PRISMA flow diagram of the review of studies identified in the main systematic review is presented in *Figure 7*.

The following sections provide a summary of the Assessment Group (AG)'s critique of the three studies reported in full-paper format,[89–92] including an assessment of the studies' quality and relevance to an NHS perspective. Details of the quality assessment implemented are included in *Appendix 14*, *Table 47*. For the four studies identified that were reported only as conference abstracts,[93–96] a brief overview is presented along with reported results. Given the limited nature of the reporting of study details, no formal quality assessment of the abstracts was undertaken.

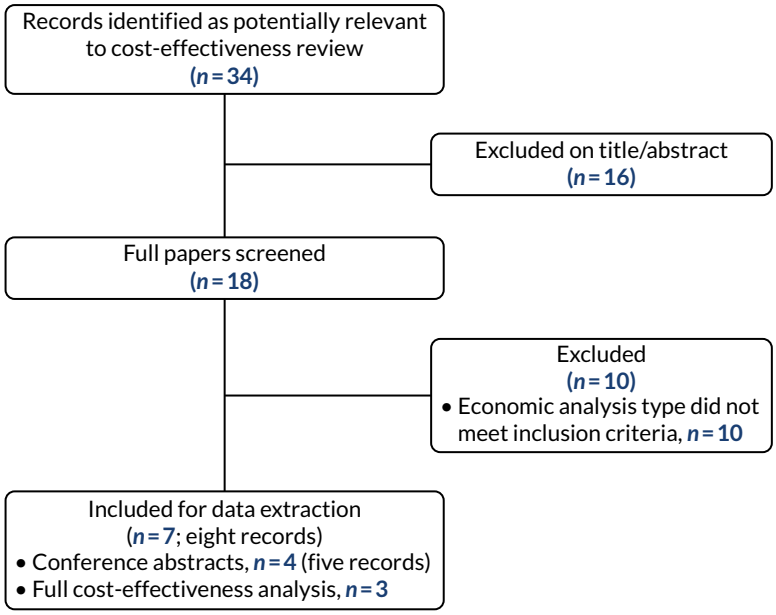

FIGURE 7 Flow diagram of the study selection process for the cost-effectiveness review.

Review of Rognoni *et al.* (2017 and 2018)[90,97]

Overview

Two studies by Rognoni *et al.*[90,97] reported on the cost-effectiveness of SIRT in HCC from an Italian heath service perspective. Both studies used the same basic model design and inputs, but investigated different treatment strategies. One study[97] compared SIRT with sorafenib in two HCC subpopulations: intermediate (BCLC B) and intermediate-advanced (BCLC C) disease. The other study[90] compared SIRT followed by TACE and possibly sorafenib with SIRT followed by sorafenib in patients with intermediate disease (BCLC B).

Both studies presented a probabilistic Markov model consisting of up to five health states: stable disease, progression, posttransplant, death from disease and death from other causes. The post-transplant health state was used only for the comparison of SIRT with sorafenib in patients with intermediate disease. Transition probabilities were drawn from three Italian oncology centres, which were compared using propensity score matching. HRQoL measures were not reported in this cohort; utilities were, therefore, derived from cost-effectiveness analysis registries. Utilities were assumed to be the same across the patient populations. Italy-specific costs were used in the model, and were derived primarily from official local tariffs and reference costs.

For intermediate-stage patients, the estimated incremental cost-effectiveness ratio (ICER) for SIRT compared with sorafenib was €3302 per quality-adjusted life-year (QALY) gained. In advanced-stage patients, SIRT was found to dominate sorafenib. These results appear to be driven primarily by the relatively low costs of the SIRT procedure relative to the acquisition costs of sorafenib, combined with significant clinical benefits of SIRT resulting in additional life-years gained (LYG). In the comparison of SIRT followed by TACE and possibly sorafenib, with SIRT followed by sorafenib, SIRT-TACE-sorafenib was found to dominate SIRT-sorafenib.

Commentary

The two studies appear to be comprehensive and well implemented, accounting for all major sources of costs and benefits, including long-term benefits in patients receiving liver transplant. However, the fitting and selection of parametric functions to survival data were poorly described and explored. Variability in cost-effectiveness estimates was explored using a one-way sensitivity analysis, showing that the results were robust to a wide range of assumptions.

However, the two studies suffered from a number of potential limitations. Foremost among these is the use of non-randomised data to produce estimates of relative effectiveness. Although propensity scoring was used to adjust for baseline imbalances, this process may have affected the results. The comparison between SIRT and sorafenib in the BCLC C subgroup is of particular concern, as a significant survival benefit was predicted for patients receiving SIRT. This is inconsistent with the results of the SARAH[19] and SIRveNIB[21] trials reported in *Chapter 3*, *Efficacy and safety of SIR-Spheres*, which show no such benefit. The HRQoL values used were generally not reflective of the population under consideration, and matched poorly with those used in previous NICE technology appraisals (TAs) in this indication. The study was also limited in its capacity to inform the present appraisal as the costs and resource use evidence reflected an Italian health-care setting, and the choice of comparators does not represent current UK practice.

Review of Rostambeigi *et al.* (2014)[91,92]

Overview

The study by Rostambeigi *et al.*[91,92] (also presented as a conference abstract) sought to assess the cost-effectiveness of SIRT versus conventional TACE in three subgroups (BCLC A, B and C) of patients with HCC from a US Medicare perspective.

The model presented was a patient simulation that followed 750 patients (split evenly between BCLC A, B and C) through a treatment pathway comprising treatment with either SIRT or TACE. The simulation was repeated for each treatment type and patient subgroup over a time horizon of 3 or 5 years. The model structure adopted is not clearly reported, but appeared to allow for disease recurrence, mortality and liver transplant.

Probabilities for each outcome were drawn from the literature for each patient subgroup according to BCLC stage. Exponential curves were used to estimate survival based on reported survival rates, with a 10% increase in mortality for 1 month following recurrence of HCC and re-treatment. Transplant rates of 29%, 16% and 5% were applied for patients in BCLC stages A, B and C, respectively, although is it unclear how this affected model outcomes. The model assumed disease 'recurrence' rates of 40%, 60% and 80% every 10 months for SIRT patients, whereas TACE patients had a recurrence rate of 60%, and could receive 4 to 10 procedures. An assumed probability of 0.5 was used for SIRT re-treatment at the beginning of every 10-month treatment interval, and patients were assumed to receive a maximum of two or three SIRT treatments depending on the scenario. Costs applied in the model were obtained from Medicare reimbursement costs; HRQoL was not considered.

The ICERs presented were estimated using an unconventional approach, calculated by dividing the incremental mean cost per month of survival (i.e. total costs divided by OS in months) by the overall incremental survival in months. The authors did not account for dominance in their calculations, presenting a number of negative ICERs without sufficient interpretation of their different meanings. ICERs in which SIRT was less costly and less effective, less costly and more effective, and more costly but less effective than TACE were presented without further distinction.

In the main analysis in which each procedure could be repeated every 10 months for up to 5 years, the AG calculated SIRT to increase mean survival by 3.80 months in BCLC C patients at a reduced cost. In the scenario in which procedures are repeated every 6 months for up to 3 years, SIRT was more effective (2.90 months incremental survival), with reduced costs compared with TACE in BCLC C patients. In all other patient groups and treatment regimens, SIRT was dominated by TACE.

Commentary

The limited reporting of the model structure and assumptions adopted prevents a detailed critique or discussion of the appropriateness of the model to estimate the relative costs and benefits of SIRT and sorafenib. A number of key structural assumptions appear to have been made arbitrarily, and poor

reporting of model inputs limits the generalisability of this study to other settings. As the resource use and costs are specific to the USA, they are unlikely to be relevant to an NHS setting. The choice of comparators and outcome measures (e.g. LYG) further limits comparison with UK practice.

Review of Marqueen *et al.* (2018)[93]

Marqueen *et al.*[93] (conference abstract only) estimated the cost-effectiveness of SIRT with yttrium-90 resin microspheres versus sorafenib in patients with advanced HCC, from a US Medicare perspective. The authors constructed a multistate Markov model (health states not reported) to estimate incremental costs and QALYs over a 5-year time horizon. Hazard rates for disease progression and death were based on a pooled analysis of individual patient data (IPD) from the SARAH[19] and SIRveNIB[21] RCTs. The clinical data used in the model were not summarised in the abstract, although the authors stated that there was no statistically significant difference in OS, and SIRT was better tolerated and with a higher quality of life than sorafenib. Trial data were also used to inform the parameter values for AEs, treatment adherence and quality-of-life utility weights.

Costs were US$135,256 versus US$90,911 and QALYs were 0.63 versus 0.60 for sorafenib versus SIRT, respectively. The resulting ICER of sorafenib was US$1,479,020 per QALY gained. A probabilistic sensitivity analysis (PSA) demonstrated that the likelihood that sorafenib would be cost-effective did not exceed 1% in cost-effectiveness thresholds up to US$200,000 per QALY. If the monthly price of sorafenib decreased from US$16,390 to US$7250, the ICER of sorafenib fell below US$200,000, and an ICER of < US$100,000 was reached if the monthly price fell below US$6500. Similar results were found using SARAH and SIRveNIB results separately.

Review of Chaplin *et al.* (2015)[94]

Chaplin *et al.*[94] (conference abstract only) conducted a cost-effectiveness analysis of TheraSphere versus sorafenib in patients with advanced HCC in the UK.[94] The authors constructed a Markov model comprising stable disease, progression and death health states, estimating incremental costs and QALYs over a 10-year time horizon. Clinical outcomes for TheraSphere and sorafenib were drawn from two separate RCTs. For TheraSphere, clinical outcomes were based on Salem *et al.*,[47] a non-randomised comparative effectiveness analysis of radioembolisation with TheraSphere ($n = 123$) versus chemoembolisation ($n = 122$). The study enrolled a range of patients, including 39% who were BCLC A, 50% who were BCLC B and 9% who were BCLC C. For sorafenib, outcomes were based on Llovet *et al.*,[98] a Phase III RCT that included 299 sorafenib patients and 303 patients on placebo, who had not received previous systemic treatment: 82% patients were BCLC C and 18% were BCLC B. Details of data synthesis were not reported in the abstract, but a comparison of median PFS and OS reported in the trial manuscripts with the model predictions suggests that the authors undertook adjustments to account for population differences.

The model estimated that TheraSphere increased TTP (6.2 vs. 4.9 months) and median survival (13.8 vs. 9.7 months). Yttrium-90 was associated with higher QALYs than sorafenib (1.12 vs. 0.85), with lower lifetime costs (£21,441 vs. £34,050). The model also included a scenario in which OS and TTP were assumed to be equivalent, in which TheraSphere remained a dominant treatment option.

Review of Parikh *et al.* (2018)[95]

Parikh *et al.*[95] (conference abstract only) estimated the cost-effectiveness of SIRT with SIR-Spheres versus sorafenib in patients with unresectable HCC and Child–Pugh class A cirrhosis, from a US payer perspective. The authors constructed a Markov simulation model. Clinical inputs for survival and AEs were derived from the SARAH[19] and SIRveNIB[21] trials. Costs were derived from a literature review, Red Book pharmacy data[99] and SEER - Medicare data.[100] Although methods for estimating clinical outcomes were not reported, the authors stated that both trials failed to demonstrate a survival difference between SIRT and sorafenib, although patient-reported outcomes were superior in the SIRT groups. The authors reported results of the model using data from the SARAH trial only, data from the SIRveNIB trial only and an analysis in which data from both studies were pooled.

In all scenarios, SIRT was associated with lower total QALYs than sorafenib was. Using data from SARAH,[19] SIRT was associated with increased costs compared with sorafenib and, therefore, sorafenib was the dominant treatment option. Using data from SIRveNIB,[21] sorafenib was associated with an ICER of >US$100,000, owing to lower SIRT costs. When combining data from both trials, sorafenib was cost-effective compared with SIRT, with an ICER of US$19,534 per QALY gained. In the combined scenario, lifetime costs were US$63,333 for sorafenib and US$61,897 for SIRT, and there were 0.88 QALYs gained for sorafenib and 0.81 QALYs gained for SIRT. The authors concluded that sorafenib is cost-effective compared with SIRT for patients with unresectable HCC, and that SIRT should not be used as first-line therapy in patients with advanced HCC who are eligible for sorafenib.

Review of Palmer *et al.* (2017)[96]

Palmer *et al.*[96] (conference abstract only) built a cost-minimisation model to evaluate the cost-effectiveness of SIR-Spheres versus sorafenib for patients with BCLC C HCC. This model assumed equal efficacy between SIR-Spheres and sorafenib based on data from the SARAH RCT.[19] AE data were collected from Llovet *et al.*[98] for sorafenib and Sangro *et al.*[69] for SIR-Spheres. Costs were derived from 'standard UK sources' and data from a UK hospital.

SIR-Spheres dominated sorafenib in this analysis, generating 0.0079 (95% CI 0.0046 to 0.0111) more QALYs than sorafenib, and providing a cost saving of £8909 (95% CI £3257 to £14,570). One-way sensitivity analyses showed that the primary drivers were time on treatment for sorafenib and the costs of work-up and administration for SIR-Spheres. The authors concluded that SIRT using SIR-Spheres is a cost-effective option for BCLC C HCC patients in the UK.

Discussion

The review of existing cost-effectiveness evidence identified three full studies along with four evaluations reported only in abstract form. The three studies reported as full texts compared SIRT with TACE, SIRT with sorafenib, and two alternative treatment sequences: SIRT followed by TACE and possibly sorafenib against SIRT followed by sorafenib. All studies reported in abstract form compared SIRT with sorafenib.

Selective internal radiation therapy versus sorafenib

Only one study comparing SIRT with sorafenib was reported as a full text (i.e. Rognoni *et al.*[89,90]), with the remainder reported as conference abstracts (i.e. Chaplin *et al.*,[94] Marqueen *et al.*,[93] Palmer *et al.*[96] and Parikh *et al.*[95]).

The Rognoni *et al.*[89,90] study has a number of important limitations, most notably the use of non-randomised evidence to estimate the relative effectiveness of SIRT and sorafenib. The survival gains achieved on SIRT in this study were not reflected in the much larger SARAH[19] and SIRveNIB[21] trials. A further limitation of the Rognoni *et al.*[89,90] study was the questionable source of utility values, which do not reflect HRQoL values used in a number of previous TAs in advanced HCC. The Rognoni *et al.*[89,90] study also adopts a non-UK perspective, which further limits the relevance of the model results to UK decision-makers.

Except for Chaplin *et al.*,[94] which used non-randomised sources of efficacy data, the conference abstracts drew data from the SARAH and/or SIRveNIB trials. This may mean that these studies are more relevant to NHS decision-making. However, their results were inconsistent. Marqueen *et al.*[93] and Palmer *et al.*[96] both reported small QALY gains in favour of SIRT with lower incremental costs. Parikh *et al.*,[95] in contrast, reported sorafenib to be more clinically effective with higher costs for sorafenib. The source of this inconsistency is unclear given that all three studies derived clinical effectiveness data from the same trials, but this may be reflective of differences in cost and HRQoL assumptions. In these three models, the differences in incremental QALYs between sorafenib and SIRT are small, suggesting that the results may be very sensitive to different assumptions around survival or HRQoL. Marqueen *et al.*[93] and Palmer *et al.*[96] noted that model predictions were sensitive to treatment cost assumptions. Palmer *et al.*[96] specifically highlighted SIRT work-up costs and time on treatment for sorafenib as particular drivers of cost-effectiveness.

Because of these inconsistencies, it is difficult to draw conclusions on the cost-effectiveness of SIRT based on existing analysis of the SARAH and SIRveNIB trials. Limited reporting also prevents meaningful validation of the assumptions and input parameters used in each model, and only Palmer *et al.*[96] was conducted from a UK perspective.

Selective internal radiation therapy versus transarterial chemoembolisation

One study, reported as a full text by Rostambeigi *et al.*,[91,92] evaluated the cost-effectiveness of SIRT versus TACE. However, the model structure and inputs used in the analysis were inadequately reported and justified. This is reflected in the AG's quality assessment (see *Appendix 5*), in which the majority of elements were scored as unclear. In particular, the source of the clinical effectiveness data used to populate the model is unclear. The evidence identified in the systematic review presented in *Chapter 3*, however, suggests that it was probably based on non-randomised comparative studies, as little RCT evidence was identified in a CTT-eligible population.

Previous National Institute for Health and Care Excellence guidance

There have been three previous NICE TAs in HCC, although none was for SIRT. These include the evaluations of sorafenib (TA474[11]), lenvatinib (TA551[12]) and regorafenib (TA555[13]). These appraisals are all for systemic therapies for the treatment of advanced unresectable HCC, which forms a subpopulation of that outlined in the scope of the present appraisal of SIRT. This section discusses the key issues and sources of data in each appraisal.

A summary of relevant NICE technology appraisals completed prior to July 2019 is presented in *Table 16*.

TABLE 16 Summary of previous technology appraisals in HCC

Characteristic	Sorafenib (TA474)[11]	Lenvatinib (TA551)[12]	Regorafenib (TA555)[13]
Model structure	Markov model, using three health states: progression free, progressed and dead	A partitioned survival model, using three health states: progression free, progressed and dead	A partitioned survival model, using three health states: progression free, progressed and dead. Cycle length of 28 days
Population	Patients with advanced-stage HCC, who have failed or are unsuitable for surgical or locoregional therapies	Untreated, advanced or unresectable HCC patients who had Child–Pugh class A status. This was in line with the NICE scope for this appraisal. The ERG evaluated efficacy results for the Western subgroup, but ultimately used the full population results	Adults with advanced, unresectable HCC who had previously received sorafenib
Intervention and comparators	Sorafenib, administered orally at a dose of 400 mg twice daily The comparator was BSC Dosing based on mean dose received in the SHARP trial,[69] assuming no wastage	The intervention was lenvatinib, which is orally administered. The starting dose was 12 mg for patients weighing > 60 kg, and 8 mg for patients weighing < 60 kg Dosing was based on mean dose received by the Western subgroup of the REFLECT trial,[12] assuming no wastage. The ERG implemented dosing based on full pack usage (no wastage) The comparator was sorafenib, administered orally at a daily dose of 800 mg	Regorafenib, administered orally at a dose of 160 mg once daily for the first 21 days of each 28-day treatment cycle The comparator was BSC, consisting of symptomatic therapies only The company used mean doses from RESORCE[101] to estimate regorafenib usage. The ERG implemented dosing based on full-pack usage (no wastage)

TABLE 16 Summary of previous technology appraisals in HCC (*continued*)

Characteristic	Sorafenib (TA474)[11]	Lenvatinib (TA551)[12]	Regorafenib (TA555)[13]
Perspective, time horizon and discounting	NHS perspective (PSS in sensitivity analysis). Time horizon of 14 years; discount rate of 3.5% applied to both costs and QALYs	NHS and PSS perspective. Time horizon of 20 years; discount rate of 3.5% applied to both costs and QALYs	NHS and PSS perspective. Time horizon of 15 years; discount rate of 3.5% was applied to both costs and QALYs
Source of clinical outcomes data	SHARP trial.[69] A Phase III trial comparing sorafenib with BSC, enrolling patients with an ECOG score of 0–2 and Child–Pugh class A liver disease	REFLECT trial.[12] A Phase III trial comparing lenvatinib with sorafenib enrolling patients with unresectable BCLC stage B (those who were ineligible for TACE) or BCLC stage C HCC, and Child–Pugh class A liver disease	RESORCE trial.[101] A Phase III trial comparing regorafenib with BSC. This study excluded patients who discontinued treatment with sorafenib due to toxicity, those with Child–Pugh class B liver disease, and those with an ECOG performance score of ≥ 2
Effectiveness extrapolation	For PFS, the company fit a log-normal model For OS, the company fit a log-normal model. Weibull was considered equally plausible by the committee	For PFS, the company fit a log-normal model to each treatment group independently. The ERG applied a gamma distribution for PFS in its base-case analysis For OS, a log-logistic function was fitted to each treatment group independently. The ERG preferred adjusted OS analyses, controlling for rates of subsequent therapy	For PFS, observed KM curves were used directly For OS, the company used a log-normal function fitted to IPD for regorafenib group in RESORCE,[101] with the relative effect for BSC modelled using a HR The ERG preferred independent Weibull functions to model OS
HRQoL	Mapping from FACT-G collected during the SHARP[69] study to a set of time trade-off utility values using a published algorithm A treatment effect was not included	Estimated based on EQ-5D-3L data collected in the REFLECT trial[12] A linear mixed model was used to generate health state utilities from the EQ-5D data, controlling for prior treatment, age, sex, geographical region, baseline EQ-5D score and baseline ECOG performance status. A treatment effect was not included. Disutilities associated with AEs were not explicitly modelled	Estimated based on EQ-5D-3L data collected in the RESORCE trial[101] A tobit regression model was fitted to the data: progression status and TEAEs were included as covariates. Treatment effect was not included as a covariate
Resources and costs	Costs and health-care resource use considered included drug acquisition, disease management and AEs Disease management costs were estimated from pooling two surveys used in the sorafenib appraisals (2007 and 2015)	Costs and health-care resource use considered included drug acquisition, disease management, AEs and end-of-life costs Unit costs were from national sources. Disease management costs were estimated from pooling two surveys used in the sorafenib appraisals (2007 and 2015)	The company's model included costs of (1) drug acquisition for regorafenib, (2) health state resource use and (3) the management of AEs. Unit costs were from national sources Resource use consisted of visits, tests and hospitalisations, and was estimated from the sorafenib resource use survey conducted in 2015, as no further sources of medical resource use data were identified The ERG preferred the use of combined 2007 and 2015 survey costs

continued

TABLE 16 Summary of previous technology appraisals in HCC (*continued*)

Characteristic	Sorafenib (TA474)[11]	Lenvatinib (TA551)[12]	Regorafenib (TA555)[13]
Time on treatment and subsequent therapies	The cost of post-progression sorafenib treatment was removed from the model, but the analysis submitted for Cancer Drugs Fund reconsideration included these costs Patients received BSC after treatment discontinuation	Time to treatment discontinuation KM data were used directly in the model to estimate the proportion of patients on treatment at a given time Subsequent therapies applied after discontinuation in the company model included sorafenib and regorafenib. The REFLECT trial[12] included other therapies post progression. The ERG preferred a scenario whereby post-progression therapy costs were removed; however, the committee concluded that it was reasonable to apply these costs as the benefits of post-progression treatment was reflected in the OS model	Discontinuation probability applied for patients while progression free and post progression, from RESORCE.[101] Progression-free: based on proportion of patients discontinuing regorafenib for more than one cycle prior to disease progression and median PFS. Post progression: based on proportion of patients who continued to receive regorafenib after disease progression and post-progression treatment rate The ERG preferred to fit a log-logistic model to the time to treatment discontinuation KM data No subsequent therapies were applied after discontinuation
AEs	Grade 3 or 4 TEAEs occurring in ≥ 10% of patients in the sorafenib arm of SHARP[69]	Grade 3 or 4 TEAEs occurring in ≥ 5% of patients in either arm of REFLECT,[12] or if identified as being clinically or economically significant by UK clinical experts (diarrhoea, asthenia and fatigue)	Grade 3 or 4 TEAEs occurring in ≥ 5% of patients in either arm of RESORCE[101]
Results (ICER, Δ£/ΔQALY)	Company base case (TA189): £64,754 Updated company base case (TA474): £39,162 DSU (TA474): between £51,208 and £71,276	Company base case: lenvatinib dominated sorafenib ERG base case: lenvatinib dominated sorafenib	Company base case: £33,437 per QALY gained ERG base case: £81,081 per QALY gained

EQ-5D-3L, EuroQol-5 Dimensions, three-level version; ERG, Evidence Review Group; FACT-G, Functional Assessment of Cancer Therapy – General; PSS, Personal Social Services; TEAE, treatment-emergent AE.

The modelling approach taken across all three appraisals was similar, with each using a model based on three health states: progression free, progressed disease and death. The sorafenib appraisal differed slightly in its approach and used a Markov model, whereas a partitioned survival modelling approach was used in the other two appraisals.

Clinical data for TA474[11] (sorafenib), TA551[12] (lenvatinib) and TA555[13] (regorafenib) were drawn respectively from the relevant pivotal trials SHARP,[69] REFLECT[12] and RESORCE.[101] Because of the availability of directly relevant RCT data, no meta-analysis was undertaken in any of the three appraisals. Modelling of clinical effectiveness was, therefore, undertaken by extrapolating available KM data. The committee's preferred approach in all three appraisals was to independently fit parametric functions to each of the treatment arms on the grounds that proportional hazards did not hold. The parametric function adopted varied across appraisals, with the log-normal and Weibull functions considered the best fitting and most clinically plausible in the appraisal of sorafenib, and the log-logistic function was considered the most appropriate in the lenvatinib appraisal. In the regorafenib appraisal, the Weibull function was considered the best fit, with the exponential and Gompertz functions being plausible alternatives.

Modelled HRQoL across all three appraisals was based on data collected in the respective pivotal trials. In each appraisal, health state utilities were determined by the presence/absence of progressive disease, with no treatment effect included. Progression-free utilities in TA474 and TA551 were similar (0.69 and 0.693, respectively). However, progressive disease values differed, with 0.71 used in TA474 and 0.63 used in TA551. Utility values used in TA555 were generally higher than those in TA474 and TA551. The progression-free utility value used was 0.81, with a utility decrement of –0.048 applied in progression. The Evidence Review Group questioned the face validity of the utility values used, noting the inconsistency with TA474 and TA551, which appraised first-line systemic therapy, whereas regorafenib is positioned as a second-line therapy used after discontinuation of sorafenib. Costs were broadly similar across each appraisal.

Time on treatment was sourced from the relevant pivotal trials through extrapolation of KM data. In TA474, time on treatment was considered to be associated with significant uncertainty, as observational data collected during the Cancer Drugs Fund period presented in the Cancer Drugs Fund reconsideration showed that median time on treatment was much shorter than observed in the SHARP trial.[69] The committee also heard from NHS England that patients are treated for a shorter period of time than was standard in 2007, trading a sizeable decrease in AEs for a small drop in effectiveness. Despite this, the committee preferred to model time on treatment based on that observed in the SHARP trial[69] to retain consistency with other clinical inputs.

Health state resource use across all three appraisals was based on two surveys of clinical experts conducted in the appraisals for sorafenib (TA189 and TA474), with unit costs updated in subsequent appraisals. Health state costs included medical staff visits, laboratory and radiological tests, and inpatient costs (including general ward, intensive care unit and accident and emergency admission). The committee preferred to pool the original and revised estimates of resource use, as it was noted that resource use data estimates varied widely.

Review of economic evidence submitted by companies

The Sirtex[102] and BTG[103] submissions included health economic evaluations assessing the cost-effectiveness of SIR-Spheres and TheraSphere for the treatment of HCC, together with fully executable health economic models. The Terumo submission[104] included a budget impact analysis but did not include any further economic evidence.

The Sirtex and BTG company submissions each present the methods and results of two separate economic evaluations that split the population potentially eligible for SIRT into two main groups. The two populations considered in each submission were (1) those eligible for CTT, referred to by Sirtex as TACE, and BTG as TAE, assumed to consist primarily of BCLC B patients, and (2) those who are ineligible for CTT, assumed to consist primarily of BCLC C patients.

Sirtex submission: conventional transarterial therapy-eligible analysis

A cost-minimisation analysis (CMA) was conducted by Sirtex to compare SIR-Spheres, TheraSphere, TACE [referred to by Sirtex as conventional transarterial chemoembolisation (cTACE) in its company submission] and DEB-TACE in the CTT-eligible population. A summary of the key features of the Sirtex model is presented in *Table 17*. A CMA assumes that the treatments being compared are equivalent in terms of their clinical effectiveness, and considers only the costs associated with each treatment. The presented analysis, therefore, compares only the respective costs associated with each technology. Sirtex's justification for implementing a CMA rather than a cost–utility analysis was the lack of comparative evidence available, and the uncertainty of the results of its NMA in this population.

TABLE 17 Sirtex model scope (CTT-eligible population)

Model component	Description
Population	The patient population that is the focus of the cost-effectiveness analysis includes patients matching the following criteria: • People with intermediate-stage (BCLC stage B) HCC, who are eligible for treatment with CTT
Intervention	SIRT: • TheraSphere • SIR-Spheres
Comparator	Established clinical management without SIRT, consisting of CTT. These are: • TACE • DEB-TACE (TACE with drug-eluting beads)
Analysis type	CMA
Economic outcome	Total treatment-related cost
Perspective	NHS and PSS
Time horizon	N/A
Discount rate	N/A

N/A, not applicable; PSS, Personal Social Services.

Evidence used to inform the company's model

The presented CMA considered the following costs: (1) initial treatment, (2) hospitalisation and (3) management of AEs.

Treatment costs of transarterial chemoembolisation and drug-eluting bead transarterial chemoembolisation

Sirtex provided three alternative scenarios for the cost of TACE and DEB-TACE. In one scenario, these costs were based on those estimated by Fateen *et al.*,[105] a single-centre retrospective database study from the UK. This study collected cost data for 101 procedures in 43 patients between 2006 and 2012 at a centre in Nottingham, UK. In this study, 25% of patients received DEB-TACE and the remaining 75% of patients received TACE. Costs reported in Fateen *et al.*[105] were for the 2012 cost year: these were inflated to 2018 costs.[106]

A second scenario used unit costs from *National Schedule of Reference Costs 2017–2018*[107] for hospitalisation, applied to resource use as estimated in the Fateen *et al.*[105] study. The mean cost per day of hospitalisation was estimated as £1757 (from Elective Inpatient, Percutaneous, Chemoembolisation or Radioembolisation, of Lesion of Liver, YR57Z), and was assumed to include the cost of delivering TACE.

A third scenario incorporated the results of the resource use survey commissioned by Sirtex, which were used to estimate the number of TACE and DEB-TACE procedures received by each patient, and the proportion of patients receiving DEB-TACE and TACE. The resource use survey was completed by five medical professionals from UK hospitals, comprising two oncologists, one hepatologist and two specialist nurses. This scenario was presented to reflect that resource use might have changed since the time that the Fateen *et al.*[105] study was undertaken. The survey estimated that a greater proportion of CTT patients receive DEB-TACE in the survey than in the earlier-conducted Fateen *et al.*[105] study (63% vs. 25%), and that, on average, there are fewer procedures undertaken for a given TACE patient (2.5 vs. 3.03) but a greater number of DEB-TACE procedures (2.83 vs. 1.43).

The costs of providing CTT, estimated as a weighted average of DEB-TACE and TACE costs, ranged from £8792.59 in the scenario based on the Fateen *et al.*[105] study (scenario 1), to £13,702.37 in the scenario incorporating the results of the resource use survey for the number of TACE and DEB-TACE procedures (scenario 3). A full breakdown of costs is provided in *Appendix 15*, *Table 48*.

Treatment costs of selective internal radiation therapy

Procedure costs relating to the administration of SIR-Spheres were assumed to comprise the device costs, the cost of work-up and the SIRT administration procedure (see *Appendix 15*, *Table 49*, for a detailed breakdown).

The acquisition cost for a single administration of SIR-Spheres and TheraSphere was assumed to be £8000.

Sirtex provided a range of scenarios to explore work-up and procedure costs, using alternative sources and assumptions to provide a range of plausible costs. Work-up costs were based on the number of work-ups and the total length of hospital stay for a work-up. SIRT procedure costs were based on the number of procedures and the total length of inpatient stay. If the hospital stay was < 1 day, the cost of an outpatient visit was instead applied.

Unit costs Unit costs of outpatient visits and the inpatient cost for one night were obtained from two different sources. These were from either *National Schedule of Reference Costs 2017–2018*[107] or a microcosting derived from a specialist nurse interview. The inpatient cost from the microcosting exercise was lower than that from *National Schedule of Reference Costs 2017–2018*[107] (£1178 compared with £1757).

Work-up resource use Two alternative sources of data were provided for the number of work-up procedures and the length of stay for the work-up. In one source, these figures were informed by a clinician survey, which did not differentiate between the resource use for TheraSphere and SIR-Spheres, which estimated a mean of 1.05 work-ups required per patient. An alternative source was from The Christie NHS Foundation Trust (The Christie NHS Foundation Trust, data on file, 2019, personal communication), which estimated a greater number of work-ups at (confidential information has been removed) per patient for SIR-Spheres and (confidential information has been removed) for TheraSphere, and longer length of stay for each SIRT, equivalent to an inpatient admission.

Selective internal radiation therapy procedure resource use Data were taken from the clinician survey and elicited from The Christie NHS Foundation Trust (personal communication) to define the number of procedures and length of stay involved in an average SIRT procedure. Sangro *et al.*[69] provided an alternative source for the number of SIR-Spheres procedures, and two studies by Salem *et al.*[25,108] were used for TheraSphere. The mean number of procedures ranged from 1.20 to (confidential information has been removed) for TheraSphere, and from 1.08 to 1.20 for SIR-Spheres. Although the SIRT procedure was provided on an inpatient basis in these scenarios, Sirtex also explored the provision of SIRT on an outpatient basis.

Adverse event costs

The unit costs applied in the CTT-eligible model are reproduced in *Appendix 15*, *Table 50*. Sirtex derived the unit costs for treating each event from previous NICE TAs, and AE rates were obtained from Salem *et al.*,[25] a Phase II RCT that compared TheraSphere with TACE in a population of early-stage HCC patients with intent to transplant. Rates of AEs for SIR-Spheres were assumed to be equivalent to those for TheraSphere. This study estimated a higher burden of AEs in CTT patients, in particular neutropenia and elevated aspartate aminotransferase. Consequently, a higher cost was applied in the model (£346 for CTT vs. £109 for TheraSphere).

Results of the economic analysis

Sirtex provided three alternative scenarios for the costs of CTT, which estimated a total cost of providing CTT ranging between £9257 and £14,167 per patient (*Table 18*).

TABLE 18 Total costs associated with providing CTT and SIRT in the CTT-eligible population

Scenario	Total costs (£)	
CTT costing		
CTT cost from literature	9257	
CTT resource use from literature with *National Schedule of Reference Costs 2017–2018*[107]	11,919	
CTT resource use from survey, literature with *National Schedule of Reference Costs 2017–2018*[107]	14,167	
	With microcosting	**With *National Schedule of Reference Costs 2017–2018*[107]**
SIR-Spheres costing		
Survey results	12,279	13,419
Survey results with outpatient procedures	12,026	12,261
The Christie NHS Foundation Trust results (personal communication)	Confidential information has been removed	Confidential information has been removed
Sangro *et al.*,[69] Salem *et al.*[25] for number of procedures, rest survey	11,185	12,222
Sangro *et al.*,[69] Salem *et al.*[108] for number of procedures, rest survey	11,185	12,222
TheraSphere costing		
Survey results	12,279	13,419
Survey results with outpatient procedures	12,026	12,261
The Christie NHS Foundation Trust results (personal communication)	Confidential information has been removed	Confidential information has been removed
Sangro *et al.*,[69] Salem *et al.*[25] for number of procedures, rest survey	13,244	14,474
Sangro *et al.*,[69] Salem *et al.*[108] for number of procedures, rest survey	15,800	17,269

A range of costing scenarios were presented for TheraSphere and SIR-Spheres based on the alternative methods for delivering the SIRT. Total costs ranged from £12,026 to (confidential information has been removed) for TheraSphere, and from £11,185 to (confidential information has been removed) for SIR-Spheres. In the scenarios that differentiated costs between TheraSphere and SIR-Spheres, TheraSphere costs were slightly higher than SIR-Spheres owing to an increased number of procedures per patient.

Rather than selecting a preferred scenario, Sirtex noted that the range of costs associated with CTT, TheraSphere and SIR-Spheres overlapped, demonstrating the comparability of treatment costs. Total costs comprised mostly those directly related to the primary treatment, with treatment for AEs and hospitalisation constituting a small proportion of total costs.

Assessment Group critique of the Sirtex conventional transarterial therapy-eligible model

Cost-minimisation analysis

The AG considered the presentation of a CMA for this population to be inappropriate and potentially misleading. Such an analysis is appropriate only if there is compelling and unambiguous evidence for equivalent efficacy between interventions. When a CMA is considered by NICE in other appraisals, it is typically accompanied by an extensive and conclusive assessment of equivalence between treatment

arms.[109–111] Clinical equivalence is a dynamic concept and any demonstration of clinical equivalence should be sustained over time. Therefore, it is important to assess whether or not the two therapies are equivalent not just in response rate, but in terms of if PFS and OS are also similar.

Results of the AG systematic review found no high-quality evidence in this population. As discussed in *Chapter 3*, *Clinical effectiveness results*, the RCTs directly comparing SIR-Spheres with TACE and DEB-TACE were very small and of poor quality, and appeared to favour the chemoembolisation procedure over SIRT in terms of survival outcomes. Although one RCT comparing TheraSphere with TACE reported longer TTP, a higher proportion of patients undergoing transplant and a small but non-significant OS benefit in the TheraSphere arm, this study enrolled a small number of patients and was rated as having a high risk of bias.[22]

Therefore, although the AG acknowledges the cited limitation in the effectiveness evidence for this population, and agrees that the development of a cost–utility model is inappropriate, the AG does not consider the identified evidence sufficient to make the strong assumption of equivalence between CTT and SIRT. Furthermore, a focus on treatment costs excludes possible important outcomes regarding people who are downstaged after treatment and become eligible to receive curative therapy, or who receive subsequent therapy after progression of disease.

Cost of treatment with conventional transarterial therapy

The cost analysis of CTT highlighted significant uncertainties in the number of CTT treatments that are typically given, and the impact on the total costs. The applicability of the available sources was limited, and included the only single UK centre collecting data between 2006 and 2012,[105] and a survey of five UK-based clinicians. These two sources were used to provide a range of the number of treatments that CTT patients might receive in practice. For TACE, the estimated range was narrow and estimated at between 2.5 and 3.03 treatments. A much wider range was, however, estimated for DEB-TACE (1.43 to 2.83). To consider the plausibility of the presented estimates, the AG searched for alternative estimates of the number of TACE and DEB-TACE procedures. The AG identified two alternative sources of representative data: a UK-based multicentre trial of DEB-TACE enrolling patients between 2010 and 2015 found that a mean of 2.18 DEB-TACE treatments were given,[22] and clinicians at a centre in the UK with experience in delivering TACE reported that patients (up to 2010) received a mean of 2.56 treatments with TACE (Dr Jai Patel, Leeds Teaching Hospitals NHS Trust, 2019, personal communication). These estimates both fall within the ranges presented by Sirtex.

Number of selective internal radiation therapy procedures

Sirtex explored the cost impact from using a range of sources to estimate the number of procedures with SIR-Spheres and with TheraSphere. Patients receiving treatment with SIRT typically receive multiple procedures on the basis of their tumour burden (i.e. bilobar involvement requiring sequential treatment visits), with patients not typically re-treated with SIRT on disease progression. Therefore, the number of procedures required would not be expected to differ between treatment arms, and the range of total treatment costs for SIR-Spheres and TheraSphere estimated by this analysis might be expected to be more similar.

Sirtex submission: conventional transarterial therapy-ineligible analysis

The cost–utility model developed by Sirtex evaluates SIR-Spheres for the treatment of HCC in patients currently ineligible to receive TACE, and assesses the incremental cost-effectiveness of SIR-Spheres compared with sorafenib, as well as lenvatinib in a scenario analysis. Clinical inputs in the model are largely based on a subgroup analysis of the SARAH trial.[19] The scope of the company's model is summarised in *Table 19*. The model uses a lifetime (15-year) time horizon and takes an NHS perspective. Costs and health outcomes are discounted at a rate of 3.5% per annum, with cost-effectiveness expressed in terms of the incremental cost per QALY gained as per the NICE reference case. Costs were valued at 2017/18 prices. The population considered in the company's model is limited to those patients who are currently ineligible to receive CTT, and focuses on a subgroup of

TABLE 19 Sirtex model scope (CTT-ineligible population)

Model component	Description

Population	The patient population that is the focus of the cost-effectiveness analysis includes patients matching the following criteria:
	• Patients with unresectable intermediate (BCLC stage B) or advanced (BCLC stage C) HCC
	  ○ For whom any TAE therapies (TAE, TACE, DEB-TACE) are inappropriate
	  ○ With or without PVT/PVI
	  ○ Without extrahepatic disease
	  ○ With a tumour burden of ≤ 25%
	  ○ And with a preserved liver function (ALBI 1)

Intervention	SIRT: • SIR-Spheres yttrium-90 resin microspheres
Comparator	Established clinical management without SIRT (including but not limited to target chemotherapy). Established clinical management is limited to systemic therapy with sorafenib or lenvatinib in UK clinical practice
Analysis type	Cost-effectiveness (cost–utility) analysis
Economic outcome	Incremental cost per QALY gained
Perspective	NHS and PSS
Time horizon	20 years
Discount rate	Annual rate of 3.5% applied to costs and QALYs

PSS, Personal Social Services.

patients with a low tumour burden and good liver function. Sirtex defines this as a maximum tumour size of 25% of the liver volume, with ALBI 1. The AG noted that this population is far narrower than the population that would be eligible for SIRT within the 'CTT-ineligible' population, and it does not match the population defined in the NICE scope. It is also important to note that this subgroup represents a post hoc subgroup analysis of the SARAH trial.[19] The company submission also presented a health economic analysis of the broader CTT-ineligible population as a scenario analysis.

Model structure

The structure of the economic model developed by Sirtex takes the form of a cohort-level partitioned survival model. The main model includes three health states: (1) progression free, (2) post progression and (3) dead. In addition to the main partitioned survival component, the model also permits patients to receive curative therapy, assuming that a proportion of patients are downstaged and receive liver transplant, resection or ablation. Patients who receive curative therapies do not enter the main model, but instead effectively move into a separate two-state model, which comprises the health states (1) alive/received curative therapy and (2) dead. The proportion of patients downstaged to receive curative therapy is based on the numbers downstaged in the low tumour burden/ALBI 1 subgroup of the SARAH trial.[19] *Figure 8* presents an overview of the model structure. Both submodels use a lifetime time horizon of 15 years and monthly model cycle with a half-cycle correction applied.

In the partitioned survival submodel, the transitions between the three health states were determined directly from the survival models of PFS and OS. Given the incomplete KM data available, parametric functions were fitted to KM curves for OS and PFS from the low tumour burden subgroup of the SARAH trial.[19] Log-normal functions were selected to model both OS and PFS, assuming independent (non-proportional) hazards between treatment groups.

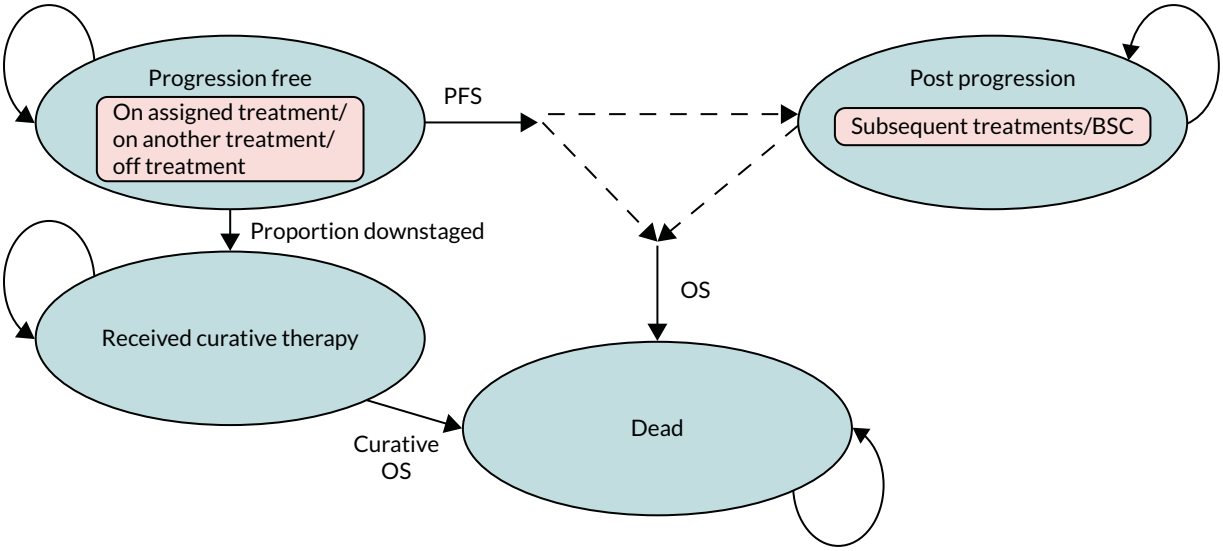

FIGURE 8 Model structure for the CTT-ineligible population. Reproduced with permission from Sirtex Medical Ltd.[102]

In the partitioned survival model, health state utilities are determined based on the presence or absence of disease and the therapy received, with utility values drawn from the low tumour burden/ALBI 1 subgroup of the SARAH trial.[19] The model does not separately account for loss of QALYs as a result of AEs, as these were assumed to be accounted for through the direct use of trial-based utility values. Utility values used for patients receiving curative therapy were the same as those for pre-progression in the SIR-Spheres arm of the main partitioned survival model.

The model includes the following costs: (1) procedural costs relating to the administration of SIR-Spheres and liver transplant, (2) sorafenib/lenvatinib drug acquisition and administration costs, (3) monitoring for participants receiving non-curative care and (4) costs associated with AEs.

The model employs the following structural assumptions:

- Health-related quality of life is determined according to the presence/absence of disease progression and the therapy received.
- Progression-free survival and OS are modelled using Weibull functions assuming independent (non-proportional) hazards.
- Survival models for PFS and OS were fitted to the low tumour burden/ALBI 1 subgroup of the SARAH trial.[19]
- Adverse events are assumed to affect costs only, with HRQoL assumed to be captured by the use of trial-based utility values.
- Utility values were assumed to differ according to therapy received in both the pre-progression and post-progression health states.
- Patients downstaged to receive curative therapy were assumed not to have recurrence of disease, with mortality outcomes determined from a US cohort study comparing outcomes for patients receiving palliative and non-palliative care.[112]

Evidence used to inform the company's model

Overall survival

Overall survival for patients downstaged and in receipt of palliative care was modelled separately, with the proportion of patients downstaged based on observed values in the low tumour burden/ALBI 1 subgroup of the SARAH trial.[19]

Overall survival for patients who are not downstaged to curative therapies in the economic model was based on observed survival in the SARAH trial,[19] using data on the low tumour burden/ALBI 1 subgroup of patients, including 37 SIRT patients and 48 sorafenib patients.

Before fitting parametric functions to the available KM data, diagnostic plots were used to assess the plausibility of assumption of proportional hazards. The plots revealed some evidence to suggest that the proportional hazards assumption may not hold, as in some instances the lines were not parallel and indeed crossed in some cases.[102] The Schoenfeld residuals, however, suggest no significant deviation from the proportion hazards assumption. Given this uncertainty, Sirtex opted to fit separate parametric functions to the KM data.

The following parametric survival models were fitted to the observed KM data: Weibull, log-normal, log-logistic, exponential and gamma functions. Assessment of the most appropriate parametric extrapolation was made with reference to statistical goodness of fit, visual fit to the observed data and assumptions made in previous TAs.[11–13] Assessment of statistical fit (see Sirtex company submission,[102] appendix F) revealed a similar statistical fit for the majority of curves, with the exponential curve observed to have the highest statistical fit. In assessing visual fit, Sirtex noted that the generalised gamma, Weibull and Gompertz curves crossed, which is not seen in the KM curves until the last few patients, whereas the log-normal and log-logistic curves did not cross. Sirtex further noted that in previous TAs of sorafenib (TA474[19]) and lenvatinib (TA551[12]), the log-logistic and log-normal curves were considered the most appropriate, and in the analysis of the SARAH[19] ITT population the log-normal distribution fitted best, in terms of both goodness-of-fit statistical criteria and visual inspection. On these grounds, Sirtex therefore selected the log-normal function for its base-case analysis. Assessment of uncertainty in curve selection was also partially explored in two scenario analyses considering the log-logistic and Weibull distributions.

Overall survival outcomes for patients downstaged to curative therapy were not drawn from the SARAH trial,[19] as OS data were censored on receipt of curative therapy. Survival outcomes for these patients were, therefore, based on a US cohort study,[112] which reported the outcomes for patients who did and did not receive curative therapy. The survival HR for downstaged patients was 0.29 (95% CI 0.18 to 0.47). To model survival in the downstaged patients, this HR was applied to the treatment-specific survival curves for SIR-Spheres and sorafenib patients. Importantly, because this HR was applied to the individual survival curves for SIR-Spheres and sorafenib, the model implies differential OS following receipt of curative therapies depending on the initial treatment received.

Progression-free survival

Progression-free survival was defined as the time from the closest date of radiological examination before the first administration of the study treatment to disease progression (per investigator assessment), or death from any cause. Because progression events were observed across patients who were and were not downstaged to receive curative therapy, a common PFS curve was assumed for all patients irrespective of whether or not they received subsequent curative therapy. Sirtex's base-case analysis drew PFS data from the low tumour burden/ALBI 1 subgroup of the SARAH trial.[19]

Assessment of the proportional hazards suggested a degree of uncertainty in whether or not this assumption holds. Assessment of statistical fit based on Akaike information criterion (AIC) and Bayesian information criterion (BIC) of the jointly fitted data found that the (assuming proportional hazards) log-logistic and log-normal, as well as the independently fitted (no proportional hazards) log-normal, distributions had the best statistical fit. Aligning with assumptions made for OS, Sirtex's base-case analysis used independently fitted log-normal distributions. Uncertainty in curve selection was partially explored in a scenario analysis in which the log-logistic and Weibull distribution were used.

Health-related quality of life

The primary source of utility data used by Sirtex was the SARAH trial,[19] which measured HRQoL using the EORTC QLQ-C30 questionnaire. There were a significant number of missing responses over the course of the study, ranging from 19% at baseline to 56.8% at 18 months, with an overall rate of missing data of 38.5%. To calculate health state utilities from this data set, the mapping algorithm by Longworth *et al.*[113] was used to generate EQ-5D scores adjusted to reflect UK population weights. Sirtex did not consider the SARAH trial[19] to show evidence of an independent treatment effect on utility, and there was no significant difference between the HRQoL of those treated with SIR-Spheres and those treated with sorafenib. The company submission,[102] however, also notes a statistically significant difference in reported global health scores between treatment arms, and applies treatment-specific utility values based on the subgroup of patients with a tumour burden of $\leq 25\%$ and ALBI 1. The values used in the base-case model are reported in *Appendix 15*, *Table 51*.

Selective internal radiation therapy procedure costs

Procedure costs relating to the administration of SIR-Spheres were assumed to comprise the device costs and cost of the work-up and treatment procedures. All patients in the SIRT arm of the model were assumed to undergo at least one work-up procedure, with 5% of patients also assumed to undergo a second work-up based on clinical opinion. To account for the fact that not all patients will go on to receive SIRT (e.g. owing to excess shunting), only a proportion of patients were assumed to receive SIRT. Sirtex's base case used the low tumour burden/ALBI 1 subgroup of the SARAH trial[19] to derive this figure. The model also permitted SIRT patients to be re-treated with SIRT. Sirtex did not consider the average number of SIRT treatments in the SARAH trial[19] to represent likely UK practice, as the SARAH trial[19] mandated separate administrations where bilobar disease was present. Sirtex instead used data from the CIRT[114] (Belgium, France, Germany, Italy, Spain and Switzerland) as well as the ENRY study showing that patients with bilobar disease typically receive a single administration of SIRT with both lobes treated simultaneously.[69] The number of SIRT administrations was, therefore, based broadly on the CIRT, with 1.20 treatments assumed per patient. Uncertainty in the number of SIRT administrations was also explored in scenario analyses based on the SARAH trial,[19] the SIRveNIB trial,[21] the ENRY study[69] and The Christie NHS Foundation Trust data (personal communication).

Costs relating to the work-up and SIRT procedures were based on *National Schedule of Reference Costs 2017–2018*,[107] with the cost of SIR-Spheres assumed to be £8000 per administration. *Appendix 15*, *Table 52*, summarises the assumptions and costs of the SIRT procedure.

Drug acquisition costs: systemic therapies

Drug acquisition costs for sorafenib and lenvatinib were taken from the *British National Formulary* (BNF).[115] Dosing of sorafenib was based on the SARAH trial,[19] assuming that 24% of patients received an 800-mg dose and 76% received a 600-mg dose. In scenarios in which lenvatinib was included as a comparator, dosing was based on TA551,[12] with 65% assumed to receive an 8-mg dose and 35% assumed to receive a 12-mg dose.[12] Duration of sorafenib therapy was based on the time-to-discontinuation curve from the SARAH trial,[19] which was extrapolated using a log-normal function. Duration of lenvatinib therapy was estimated by applying a HR to the sorafenib time-to-discontinuation curve taken from TA551.[12]

Subsequent treatments

Modelled subsequent treatments without curative intent were based on expert elicitation, as the subsequent treatments received in the SARAH trial[19] were not considered reflective of NHS practice. Drug costs were taken from the electronic market information tool (eMIT)[116] and the BNF.[115]

For patients downstaged to receive curative therapies, the modelled therapies were based on those received in the ITT population of the SARAH trial,[19] consisting of resection, liver transplantation and tumour ablation. The proportion receiving each type of therapy is summarised in *Appendix 15*, *Table 53*.

Costs of resection were based on NICE TA474,[11] and costs of ablation and liver transplantation were based on *National Schedule of Reference Costs 2017–2018*.[107]

Health state costs

Resource use estimates were based on a survey of clinical experts, and included medical staff contacts [e.g. general practitioner (GP) appointments], diagnostic procedures, inpatient care and Personal Social Services (PSS) contacts. Unit costs were derived from *National Schedule of Reference Costs 2017–2018*.[107] Total costs by health state are reported in *Appendix 15*, *Table 54*.

Adverse event costs

The costs of grade 3 or 4 TRAEs experienced by ≥ 5% of the population were modelled, with rates drawn from the SARAH[19] and REFLECT[81] trials. Costs for each AE were sourced from previous TAs and inflated to the 2018 cost year as appropriate. See *Appendix 15*, *Table 55*, for a summary of included AE costs.

Model results

The headline results presented in the Sirtex company submission[102] are based on the deterministic version of the model. Uncertainty surrounding model parameters was explored using deterministic sensitivity analysis (DSA) and PSA. The probabilistic results were estimated from 1000 Monte Carlo samples. Uncertainty was represented using tornado diagrams, cost-effectiveness planes and cost-effectiveness acceptability curves (CEACs).

Table 20 presents the base-case estimates of cost-effectiveness using the list price for sorafenib. Based on the probabilistic version of the company's model, SIR-Spheres are expected to generate an additional 0.682 QALYs at an incremental cost of –£1979 compared with sorafenib; SIR-Spheres were, therefore, estimated to be dominant, producing greater health benefits at lower overall cost. The deterministic version of the model produces similar results, with SIR-Spheres estimated to dominate sorafenib.

Figure 9 presents the results of the company's DSA. The most influential parameters (of those assessed by the company) relate to predicted OS (SIR-Spheres and sorafenib) and the proportion of patients downstaged to receive curative therapy. Additional scenario analyses presented by the company showed that the estimated ICER was generally robust to a range of alternative assumptions, including alternative extrapolations of survival data. However, this analysis also showed that estimated ICERs increased very significantly when the source of effectiveness estimates was changed from the low tumour burden/ALBI 1 subgroup to the ITT or per-protocol population from the SARAH trial,[19] which yielded ICERs of £58,763 and £680,276 per QALY gained, respectively.

TABLE 20 Sirtex base-case results (CTT-ineligible population)

	Absolute		Incremental		
Treatment	QALYs	Costs (£)	QALYs	Costs (£)	ICER (£)
Probabilistic model					
SIR-Spheres	2.009	24,456	0.682	–1979	Dominant
Sorafenib	1.408	26,435			
Deterministic model					
SIR-Spheres	1.982	29,143	0.601	–1784	Dominant
Sorafenib	1.381	30,927			

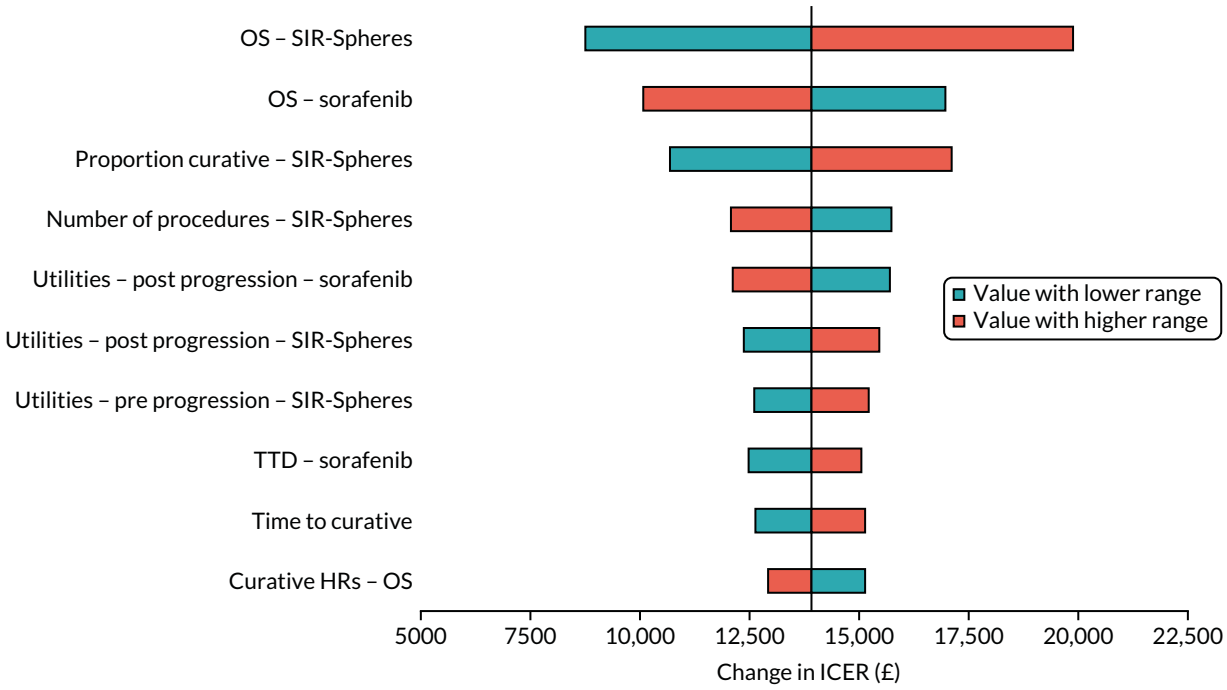

FIGURE 9 Sirtex DSA: tornado diagram. Reproduced with permission from Sirtex Medical Ltd.[102]

Critique of the Sirtex conventional transarterial therapy-ineligible model

Relevance of modelled population

The company's health economic analysis is limited to a subpopulation of patients with a tumour burden of $\leq$ 25% and with preserved liver function (ALBI 1). The company cited clinical opinion and published literature in its justification for focusing on this group, stating that the ITT and per-protocol population recruited to the SARAH trial[19] was unreflective of that eligible in the UK, while also highlighting that the trial included patients with high tumour volume, PVT and poor liver function. The company also outlined that this subpopulation increased the probability of receiving SIRT and the probability of going on to access curative therapy, citing figures from the SARAH trial.[19]

Consultation with the AG's clinical experts confirmed that this subgroup could be identified prospectively and treated with SIRT. However, they also noted that ALBIs are not routinely used to assess liver function in UK practice, and that this definition did not represent a widely accepted clinically distinct subgroup of patients.

The AG is further concerned that the selection of this subgroup is based on a post hoc analysis of a relatively small subgroup of the SARAH trial,[19] representing < 20% of the total trial population. Comparison of the results for this subgroup on key outcomes, such as PFS and OS, revealed no statistically significant differences between this group and the remaining population. Furthermore, the randomisation procedure for the SARAH trial[19] did not stratify by these baseline characteristics, increasing the risk of baseline imbalances. This can be observed in the sample size of this group between treatment arms, with 37 patients in the SIRT arm and 48 patients in the sorafenib arm. A further consequence of using this subgroup is that potentially relevant data from the SIRveNIB trial[21] cannot be used, as data on this subgroup were not available to the company. This is important for two reasons: (1) it reduces the available sample size with consequences for precision and (2) it does not allow for a confirmatory analysis of the PFS and OS benefits observed in this subgroup.

The AG is, therefore, concerned that the purported treatment effects in this subgroup are potentially an artefact of imbalances in characteristics between treatment arms. Available data do not allow further analysis to establish the validity of the observed PFS and OS gains in this subgroup.

Model structure and clinical plausibility of downstaging

The company's model allows a proportion of patients to move on to receive curative therapy. This is a significant driver of the model results, as 66% of incremental QALYs are generated by patients who received curative therapies.

The SARAH trial[19] was used to support the downstaging paradigm used in the model, in which a small number of patients went on to receive curative therapy. The plausibility of downstaging at such high rates in UK practice is unclear. The AG was advised that downstaging of patients with advanced HCC to transplant and other curative options is rare in UK clinical practice, with very few if any of these patients receiving curative therapies. It is also notable that the SIRveNIB trial,[21] which recruited a similar population, makes no mention of any patients going on to receive curative therapy. Similarly, none of the previous TAs that assessed systemic cancer treatments for advanced HCC modelled the possibility of curative therapies. The AG is, therefore, concerned that the very sizable benefits resulting from curative therapy would not be realised in practice, and that the rarity of downstaging means that any resulting incremental benefits are subject to very considerable uncertainty.

Modelling of overall survival

The company fit independent parametric survival functions to the observed data from the SARAH trial.[19] This method makes fewer assumptions than a treatment–covariate-based approach, and is in line with NICE DSU guidance on survival analysis.[117] However, the AG does not accept the company's rationale for selecting the log-normal curve, which was based primarily on visual fit and its use in previous HCC appraisals. The AG notes that the log-normal is the most optimistic of all the fitted parametric curves, and has among the worst statistical fit. The log-normal also has a much longer tail, and, in the AG's view, fits poorly to the tail of the observed data for the SIR-Spheres arm of the SARAH trial.[19] Clinical advice to the AG indicated a preference for the Weibull function, which predicts substantially shorter survival gains and also has better statistical fit.

In addition to the above, the AG is concerned that the parametric functions were fitted to the observed data that had not been censored to exclude those patients downstaged to receive curative therapy. In the economic model, the outcomes for these patients are modelling independently and, therefore, using the uncensored data means that the OS benefits experienced by these patients are double-counted. The impact of this double-counting is significant, and leads to a substantial overestimation of survival gain. For example, based on a log-normal extrapolation (used in the Sirtex base case) and using the uncensored data, estimated OS gain on SIR-Spheres is 8.27 months. Using the log-normal function on the same data censored for downstaging results in a much reduced predicted OS gain of 1.55 months.

Further to the above issues regarding the plausibility of downstaging, the AG has concerns around the methods used to model the OS benefits associated with curative therapy. Postcurative OS is modelled by using the HR from the Kanwal *et al.*[112] cohort study to the OS curve for each treatment. This HR is assumed to reflect the improvement in survival outcomes post curative therapy. The application of this HR is treatment specific (i.e. is applied to the SIR-Spheres OS curve for SIR-Spheres patients and to the sorafenib OS curve for sorafenib patients). This implies that OS postcurative therapy will differ depending on the initial treatment received, and thus favours SIR-Spheres. Expert advice received by the AG, however, considers this implausible and that outcomes will be the same post curative therapy regardless of previous therapy received.

Furthermore, the application of a HR to the log-normal curve is inappropriate, as the log-normal function is an accelerated failure time model and does not make assumptions about proportional

hazard assumptions. Consequently, survival times are considerably over estimated. The AG also questions the appropriateness of the HR of 0.29 used by the company, noting that this figure was not based on the primary analysis presented in the cited study, but on a scenario analysis in which classification of patients was based on both BCLC stage and ECOG performance status.

Modelling of progression-free survival

The company's approach to modelling PFS was similar to that of modelling OS, with independent parametric survival functions fitted to the observed data.

The AG is satisfied that the company's approach of using independent curves was appropriate given the presented evidence to support the non-proportionality of hazards. The AG, however, questions the appropriateness of fitting parametric functions to PFS data at all, given that the available KM data are all but complete; no patients remain at risk in the sorafenib arm and only one remained in the SIRT arm. The company could, therefore, have used the observed data directly, avoiding any uncertainty in the choice of parametric function.

The AG is also concerned that the modelled data were not censored for downstaging events and, therefore, double-count patients who were downstaged to receive curative treatment. As with OS, this results in PFS gains being overestimated, although to a lesser degree than OS. Mean PFS gain assuming a log-normal function was 3.7 months using the uncensored data and 2.35 months using the censored data.

Concerns regarding costs of selective internal radiation therapy

It is assumed in the Sirtex model that patients with bilobar tumours receive SIRT in both liver lobes during the same treatment session. This is in contrast with how patients were treated in the SARAH trial,[19] which mandated that patients receive separate treatments with a delay between the first and the second administration. Sequential treatment is implemented to mitigate the risk of REILD, which is more likely to occur if both lobes are treated simultaneously. The company put forward evidence from the European CIRT, and suggested that (confidential information has been removed).

The impact of this assumption is to reduce the costs of providing SIR-Spheres, as sequential treatment involves additional administration and acquisition costs. However, clinical advisors to the AG disagree with the assertion that simultaneous treatment would be implemented in the UK, and contend that in UK practice it is likely that sequential treatment would be used as per the SARAH trial.[19] Furthermore, the AG notes that, although the company adjusts costs to account for the use of simultaneous treatment, no corresponding adjustment is made to health outcomes to account for the increased risks associated with simultaneous treatment.

Failed work-up procedures

In the Sirtex model, a proportion of patients are assumed to fail the work-up procedure and are thus ineligible to receive SIR-Spheres. The proportion of patients receiving work-up who do not go on to receive SIRT was drawn from the low tumour burden/ALBI 1 subgroup of the SARAH trial,[19] which was substantially lower than for the population as a whole (8.1% vs. 18.6%). The AG is concerned about the appropriateness of this figure, given the post hoc nature of the analysis. The primary reason patients become ineligible for SIRT following work-up is a high rate of shunting of radioactive material to the lungs. Although this may be plausibly linked to tumour volume and liver status, any such association has not been demonstrated, and it is not clear that the proportion of patients who experience excessive lung shunt will vary substantially between patient groups.

Furthermore, the company's model assumes that patients who fail work-up will move to the sorafenib arm of the model. The AG considers this inappropriate as only 62% of patients in the SARAH trial[19] who failed work-up subsequently received sorafenib. The outcomes of patients in the SARAH trial[19] who received work-up but no SIRT were inferior to those who successfully received SIR-Spheres or

were randomised to the sorafenib arm. Assuming that patients who fail work-up receive sorafenib outcomes is therefore likely to overestimate the PFS and OS for those allocated to receive SIR-Spheres.

Subsequent therapy costs

The company noted in its submission that the subsequent treatments received by patients in the SARAH trial[19] included a number of therapies (e.g. capecitabine and doxorubicin) not used in UK practice. The treatments received following primary therapy in the model were, therefore, based on a survey of 12 clinicians instead.

The AG considers the proportions of patients receiving subsequent therapies in the model to be subject to substantial uncertainty, and notes that these differ substantially from those reported in the SARAH trial.[19] The proportion of patients assumed to receive sorafenib following SIR-Spheres is higher than that observed in SARAH,[19] as is the proportion of patients receiving further treatments post sorafenib. The AG also notes that post-sorafenib treatment is based on the ITT population of the SARAH trial[19] and, therefore, does not reflect the modelled low tumour burden/ALBI 1 subgroup. Given that the low tumour burden/ALBI 1 subgroup represents a particularly healthy population, it may be anticipated that a much higher proportion of these patients would go on to receive subsequent systemic therapies. As no figures on subsequent therapy in the low tumour burden/ALBI 1 subgroup are reported, this cannot be verified.

Duration of subsequent sorafenib and lenvatinib therapy was drawn from the REFLECT trial,[12] and subsequent regorafenib was based on the RESORCE trial.[101] The approach taken to define time on treatment was inconsistent, as median values were used for sorafenib and lenvatinib, whereas a mean value was used for regorafenib. The AG considers mean values more appropriate than the medians used by the company, as the aim of the model is to calculate the mean costs of subsequent therapy. The AG is also concerned that the REFLECT trial[12] considers the use of sorafenib and lenvatinib in a first-line setting, particularly as this implies that patients receiving sorafenib as a subsequent therapy will receive treatment for much longer than those who received it as a first-line therapy. The AG, therefore, considers that these values are likely to overestimate time on treatment, and that it may be better to base duration of subsequent therapy on the RESORCE trial,[101] which considers systemic therapy use in a second-line setting.

Omission of palliative care costs

The Evidence Review Group notes that the company model does not include end-of-life costs to account for palliation at the end of life. However, the impact of this omission is small, as fewer than 1% of patients remain alive at the end of the modelled time horizon, meaning that nearly all modelled patients incur this cost.

BTG submission: conventional transarterial therapy-eligible analysis

For the comparison with transarterial therapies, the company presented a cohort-based Markov model, comparing TheraSphere, SIR-Spheres and QuiremSpheres with TACE (referred to by the company as cTACE), DEB-TACE and TAE (referred to by the company as bland embolisation). Outcomes were assessed over a time horizon of 20 years using 4-week cycles, and were discounted at a rate of 3.5%. The scope of the company's model is summarised in *Table 21*.

Model structure

The model presented by BTG for the CTT-eligible population was based on a Markov structure, and contained the following health states: (1) watch and wait, (2) pre transplant, (3) post transplant (a series of three tunnel states), (4) no HCC post transplant, (5) pharmacological management and (6) dead. The model schematic is illustrated in *Figure 10*.

TABLE 21 BTG model scope (CTT-eligible population)

Model component	Description
Population	The patient population that is the focus of the cost-effectiveness analysis includes patients matching the following criteria: • People with intermediate-stage (BCLC stage B) HCC, who are eligible for treatment with CTT
Intervention	SIRT: • TheraSphere • SIR-Spheres • QuiremSpheres
Comparator	Established clinical management without SIRT (including but not limited to target chemotherapy). The target chemotherapies are: • TACE • TAE • DEB-TACE
Analysis type	Cost-effectiveness (cost–utility) analysis
Economic outcome	Incremental cost per QALY gained
Perspective	NHS and PSS
Time horizon	20 years
Discount rate	Annual rate of 3.5% applied to costs and QALYs

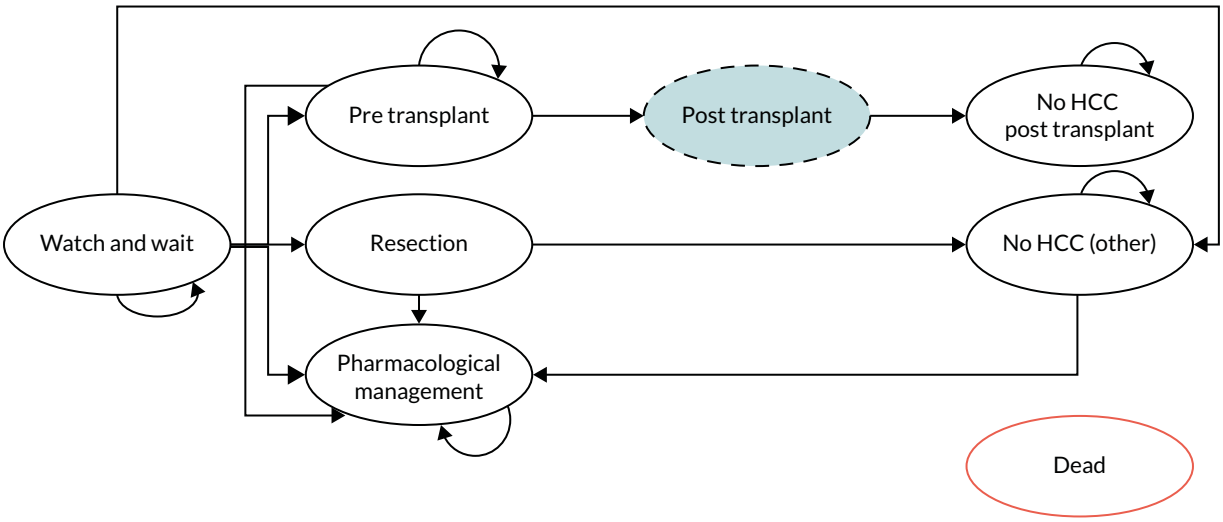

FIGURE 10 Model structure for the CTT-eligible population. Reproduced with permission from BTG Ltd.[103]

Patients who are eligible for SIRT enter the model in the 'watch and wait' health state, following initial treatment. Patients remain in this state until they (1) are downstaged and become eligible for transplant, moving on to the pre-transplant state (equivalent to a transplant waiting list), (2) transition to the pharmacological management state owing to not entering remission and being ineligible for liver transplant, or (3) die.

Although the model includes the functionality for patients to receive resection after being downstaged or achieving remission, these transitions are not included in the base-case analysis.

The pre-transplant state captures the time when patients are on the donor organ waiting list. Patients remain in this state until they (1) receive a transplant, and move to the post-transplant state, (2) experience disease progression or become ineligible for a liver transplant, after which they move to the pharmacological management state, or (3) die.

Following transplant, patients spend a single cycle in each of the post-transplant states before arriving in the no-HCC post-transplant state, where they remain until death. The three tunnel states allow for differing resource use over the time following the transplant. In addition, the model assumed that patients would not experience a tumour recurrence after transplantation.

Patients entered the pharmacological management pathway from either the 'watch and wait' health state or the pre-transplant health state. Patients remain in this health state until death, although the impact of further disease progression is implicitly captured by assuming a 50 : 50 mix of patients who are in a pre-progressed or a progressed HCC state. This split is used to estimate the mean utility value and treatment-related costs. The patients in the pre-progression part of this health state received either sorafenib (33%) or BSC (67%), and the patients in the progression portion of this health state received BSC.

Evidence used to inform the company's model

Downstaging outcomes

In this model, it was assumed that the impact of treatment with SIRT compared with CTT was limited to differences in the likelihood of patients being downstaged and becoming eligible for curative therapy.

Non-mortality outcomes for the 'watch and wait' health state were estimated from a single-centre, non-randomised comparison of TACE and TheraSphere patients.[118] The study was undertaken in a population of unresectable HCC patients who did not meet the Milan criteria[9] at presentation, specifically including patients who were of T3 United Network for Organ Sharing (UNOS) status. This is defined as patients with either a single nodule of > 5.0 cm or two or three nodules, at least one of which is > 3.0 cm in size,[119] and downstaging was defined as a decrease in the maximal tumour dimension to 3.0 cm.

The probability of remaining in the watch and wait health state for all therapies was estimated by the company using the median time to downstaging in the TheraSphere arm of the Lewandowski *et al.*[118] study. The company assumed that the median time to downstaging represented the median time to 'prognosis' (i.e. either to downstaging or to pharmaceutical management). The median time to downstaging in the study for TheraSphere patients was 3.1 months; the median time to downstaging in the TACE arm of the study had not been reached. The company converted the median time of 3.1 months to a per-cycle probability of leaving the watch and wait health state of 18.6%, resulting in a per-cycle probability of remaining in this health state of 81.4%.

Of the proportion who leave the watch and wait health state in each cycle, the company used the probability of downstaging from the Lewandowski *et al.*[118] study to estimate the transition of patients to the pre-transplant state. The remaining living patients entered the pharmacological management health state. The study reported a probability of downstaging from TheraSphere treatment of 58% (25/43), compared with 31% (11/35) downstaged from TACE.

The efficacy of SIR-Spheres and QuiremSpheres was assumed to be equal to that of TheraSphere, and the efficacy of DEB-TACE and TAE was assumed to be equal to that of TACE.

Owing to a lack of data specific to this outcome, the probability of death in each model cycle for the 'watch and wait' health state was assumed to be equivalent to that of patients on the wait list, which was estimated from a cohort of NHS patients awaiting liver transplant (see *Transplant wait list outcomes*). The mortality rate was assumed to be equal between all treatment arms. The greater

predicted benefits of SIRT in this model are, therefore, entirely attributable to a greater proportion of patients being successfully downstaged.

Appendix 15, *Tables 56* and *57*, summarise the transition probability values and mortality rates, respectively, used in the model.

Transplant wait list outcomes

The probability of successfully receiving a transplant once on the wait list was calculated by the company using the median wait time of 130 days for a liver transplant in the UK.[120] This data set is based on a cohort of 2706 NHS patients who were registered for a liver transplant between April 2013 and March 2016, and is not specific to an indication of HCC. This was converted to a per-cycle probability of 13.9%. The probability of transplantation was not conditional on initial treatment.

Patients could transition from the pre-transplant state to pharmacological management, in the case that a patient becomes ineligible for transplant while on the wait list. The probability of this happening was informed by clinical advice to the company, with 16 cases of patients leaving the wait because of disease progression for every 103 transplants (National Audit for Liver Transplant, incomplete source provided by the company).

Mortality in the pre-transplant wait list health state was estimated from a figure quoted in an NHS service specification for Liver Transplantation Service in Adults,[121] in which 'up to 18% of patients die while on the liver transplant waiting list' (reproduced with permission; contains public sector information licensed under the Open Government Licence v3.0), and converted to a per-cycle mortality rate using the median time to transplant of 130 days.

Pharmacological management outcomes

Patients entering the pharmacological management health state are assumed to remain there until death. The mortality rate applied was based on the median OS of BSC patients reported in the NICE sorafenib submission (34.4 weeks).[11] Per-cycle mortality was estimated assuming that OS followed an exponential distribution; the applied per-cycle mortality rate was 7.7%. This rate was applied to patients in this health state regardless of their initial treatment.

Post-transplant outcomes

Mortality in the three cycles (12 weeks) following transplant was estimated using data from a study of early-stage HCC patients, Bellavance *et al.*,[122] which reported a 30-day mortality probability of 1.5%.

The post-transplant mortality rate beyond these three cycles was assumed to be lower, and was estimated from NHS 5-year survival rates following transplantation[120] of liver patients who had a transplant between 2010 and 2012, which was estimated at 81%. These data reflect a general liver transplant population and are not specific to those who have HCC. Furthermore, for the patients in the population who did have HCC, they are also not specific to patients who had been downstaged after having previously been ineligible for transplant before active treatment for HCC. The company justified the assumption that the mortality rates for a downstaged population can be assumed to be equivalent to a population who were not originally downstaged, on the basis of a systematic review by Gordon-Weeks *et al.*[123]

Adverse events

For TheraSphere and SIR-Spheres, data on grade 3 and 4 TRAEs were sourced from a systematic review of AEs.[79] Event rates for QuiremSpheres were assumed to be the same as for SIR-Spheres. Rates of TRAEs for TACE and DEB-TACE were sourced from a RCT of DEB-TACE versus TACE in HCC.[58] The company's model included severe TRAEs that occurred in > 5% of patients in at least one arm.

Total TRAE utility decrements and treatment costs were applied in the first model cycle. The estimates of utility decrements were based on the assumption that grade 3 and 4 AEs were associated with a utility decrement of 0.012, which was multiplied by AE rates reported for each event. The total TRAE disutility for TheraSphere, SIR-Spheres, QuiremSpheres and TACE was estimated as −0.002, with −0.009 for TAE and 0.000 for DEB-TACE. Total TRAE costs ranged from £5.59 for DEB-TACE, to £111.33 for SIR-Spheres, and £384.15 for sorafenib. Further details of TRAE rates and associated costs are provided in *Appendix 15*, *Tables 58* and *61*, respectively.

Health-related quality of life

BTG drew on a variety of external sources for the utility values in its economic model (see *Appendix 15*, *Table 59*). Utility values for all health states with the exception of the post-transplant tunnel states were the same as the pre-progression values used in the TA551[124] submission for lenvatinib (equal to 0.75), which were estimated from EQ-5D data collected from patients in the REFLECT trial.[81] The utility applied to the 'pharmacological management' state is taken to be an average of the pre-progression and post-progression health state values, as BTG states that this population comprises patients in both progression states equally. Post-transplant utilities were derived from a study by Lim *et al.*,[125] which used an average of literature-derived utilities equal to 0.69. A scenario analysis was carried out using significantly lower pre- and post-liver transplant utilities from Ratcliffe *et al.*;[126] however, these values were taken from a primarily non-HCC population.

Utilities were adjusted according to age and gender norms reported in Kind *et al.*;[127] however, this adjustment was applied incorrectly, which resulted in patients experiencing a much lower HRQoL than reported in the cited sources. When this was highlighted to the company, it stated that this was intentional, and considered the use of lower utility values appropriate and consistent with methods reported in Kind *et al.*[127]

Costs of selective internal radiation therapy treatment

Procedure costs relating to the administration of SIRT were assumed to comprise microsphere (SIRT) acquisition costs, the cost of the work-up and procedure costs relating to the administration of SIRT. The mean number of SIRT treatments per patient was informed by an elicitation exercise undertaken by BTG. Each patient was estimated as having an average of 1.2 SIRT treatments, with one work-up per patient. Only patients who are eligible for SIRT enter the model, and so the costs of work-ups that did not result in treatment with SIRT were not included.

The work-up procedure costs were based on a microcosting from The Christie NHS Foundation Trust, Manchester, and were estimated as being £467.91. These costs included the time of the personnel involved with the work-up (a technician, clinical scientist and radiologist) and a macroaggregated albumin (MAA) body SPECT. The AG requested additional details of this microcosting; however, little further granularity was provided. In addition, BTG identified further relevant cost items in the work-up procedure, which increased the cost to £860.32 per work-up. The company assumed that the resources required for the work-up associated with TheraSphere, SIR-Spheres and QuiremSpheres would be the same.

Costs relating to the administration of the SIRT work-up and the SIRT procedure were based on *National Schedule of Reference Costs 2017–2018*,[107] and the cost of each SIRT was assumed to be £8000 per procedure. Further details are provided in *Appendix 15*, where *Table 60* summarises the assumptions and costs of the SIRT work-up procedure and *Table 62* summarises the associated unit costs.

Treatment costs of conventional transarterial therapy

Each patient in the TACE and TAE arms was assumed to have three initial treatments in their respective arms, and patients in the DEB-TACE arm had an average of 1.5 initial treatments. The unit cost and the frequency of their use was informed by clinician input.

The cost of administration involved in each CTT was assumed to be captured in the Healthcare Resource Group (HRG) code for the embolisation procedure (£2790, *National Schedule of Reference Costs 2017–2018*,[107] HRG code YR57Z).

Second-line treatment

After patients move into the pharmacological management health state, they were assumed to receive sorafenib (33% of patients) or BSC (67% of patients). Patients remain in this state until death. The unit cost of sorafenib was obtained from the BNF,[115] with the total per-cycle cost estimated assuming a posology of 400 mg twice daily. It was assumed that sorafenib would not be associated with administration costs and that patients would orally self-administer this treatment. It was unclear whether or not the costs of treating AEs associated with sorafenib treatment were captured within the model. Costs associated with BSC were assumed to be captured within the health state resource use.

Health state resource use

Owing to an absence of evidence from published literature for resource use for the CTT-eligible health states, expert opinion was sought from The Christie NHS Foundation Trust (see *Appendix 15*, *Table 63*, for a summary of health state costs). These consisted of the following:

- physician visits (oncologist, hepatologist, Macmillan nurse, gastroenterologist, radiologist, clinical nurse specialist and palliative care physician)
- laboratory tests [alpha-fetoprotein test, liver function test, international normalised ratio (INR), complete blood count, biochemistry and endoscopy]
- radiological tests [computerised tomography (CT) scan, MRI scan and ultrasound scan]
- hospitalisation
- hospital follow-ups (specialist, GP and nurse)
- transplant aftercare (immunosuppressants).

Unit costs for each of these items, plus the cost of a transplant procedure, were obtained from national sources.[106,107]

The AG requested additional details of how these resource use estimates were obtained. BTG clarified that resource use estimates were provided by a single clinical expert whose role is consultant interventional radiologist at a centre in the UK that uses SIRT. Opinion was elicited via an unstructured telephone conversation, and the estimates were given verbally and were entered directly into the model; no transcripts of this conversation were collected. Therefore, the AG cannot verify the estimation of the resource use inputs.

Additional one-off costs were applied at the point of progression, relating to laboratory and radiological tests (estimated as £95.32 in total) and were obtained from TA555.[13]

Palliative care costs

The company's model also included a cost of £8191 to account for costs of palliation at the end of life, which was applied on death. This was derived from a joint Nuffield Trust and Marie Curie report into end-of-life cancer care and inflated to 2017/18 prices.[128]

Model results

Base-case results

Results of the base-case analysis are summarised in *Table 22*. In the company's main analysis, TheraSphere, SIR-Spheres and QuiremSpheres were associated with virtually identical numbers of QALYs, owing to the assumption of equal efficacy between interventions. They were all estimated to have similar total costs, with TheraSphere estimated to have marginally lower costs owing to lower rates of AEs requiring treatment.

TABLE 22 Results of the CTT-eligible population analysis

Treatment	Total costs (£)	Total QALYs	ΔCosts (£)	ΔQALYs	ICER (£)
Probabilistic analysis (estimated by the AG)					
DEB-TACE	39,505	1.377	–	–	–
TAE	43,634	1.384	4129	0.007	621,795
TACE	43,525	1.373	4020	−0.004	Dominated
TheraSphere	57,334	2.089	17,829	0.712	25,051.73
QuiremSpheres	57,395	2.092	17,890	0.715	25,032.69
SIR-Spheres	57,415	2.093	17,910	0.716	25,008.53
Deterministic analysis					
DEB-TACE	39,435	1.393	–	–	–
TAE	43,470	1.392	4035	−0.001	Dominated
TACE	43,488	1.393	4053	0.000	Dominated
TheraSphere	57,338	2.119	17,903	0.726	24,647
QuiremSpheres	57,361	2.119	17,925	0.726	24,647
SIR-Spheres	57,361	2.119	17,925	0.726	24,647

Similarly, for TACE, DEB-TACE and TAE, marginal differences were observed owing to assumed differences in AE rates and unit costs of treatment.

DEB-TACE was estimated as being the strategy with the lowest costs owing to the fewer procedures required, and was used as the reference treatment in the incremental analysis. This resulted in an ICER of £24,647 for each of the SIRT versus DEB-TACE, and TACE and TAE being dominated versus DEB-TACE.

The probabilistic version of the model produced similar results, with the ICER relative to DEB-TACE being £25,052 per QALY.

Probabilistic results

Uncertainty surrounding model parameters was explored using scenario analyses and PSA; the executable model also included a number of DSAs that were not presented in the company submission or appendices. The company's probabilistic results were estimated from 1000 Monte Carlo samples and were presented using CEACs and cost-effectiveness acceptability frontiers (CEAFs) only, with no ICERs from the probabilistic model presented in the company submission.

Figure 11 presents the results of the company's PSA. Up to a threshold of approximately £25,000 per QALY, the company model estimated the treatment with the highest likelihood of being cost-effective to be DEB-TACE. After this point, the probability of being cost-effective was highest for the three SIRTs, which had similar probabilities of cost-effectiveness.

Scenario analyses

Table 23 presents the results of the company's scenario analysis. The most influential parameters, of those assessed by the company, relate to the proportion of patients who transition to resection, and the proportion of patients who were downstaged after treatment with TheraSphere. Although the amount by which the proportion of patients was varied was arbitrary, and the ICER does not specifically represent a potential upper bound, this analysis showed that the model was most sensitive to this parameter.

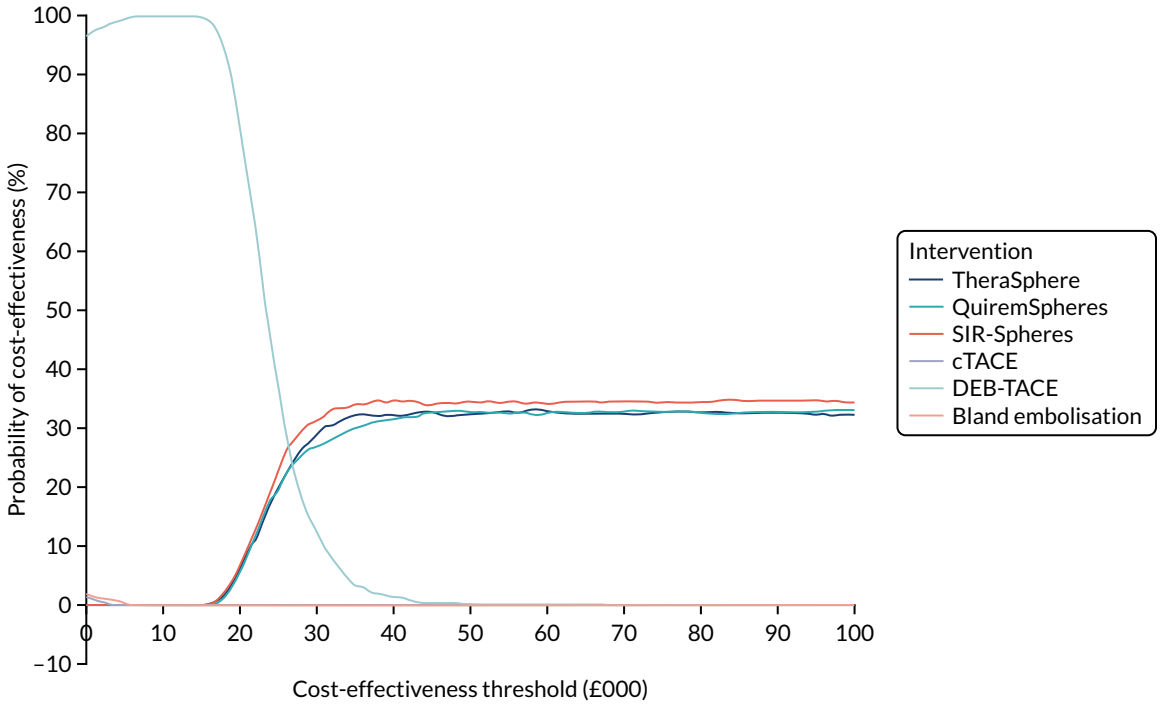

FIGURE 11 Cost-effectiveness acceptability curve (CTT-eligible population). Reproduced with permission from BTG Ltd.[103]

TABLE 23 Results of scenario analyses in the BTG CTT-eligible model

Scenario	ICER (£)
CTT-eligible scenarios: base case	***24,647***
50% discount on TheraSphere	18,039
TheraSphere treatment free when more than one treatment needed	21,676
50% of downstaged patients transition to resection rather than transplant	31,112
Removal of SIRT work-up costs	23,773
Alternative utility values	25,003
Alternative downstaging rates for SIRT (relative efficacy of SIRT decreased vs. TACE/TAE)	38,203
Alternative downstaging rates for SIRT (relative efficacy of SIRT increased vs. TACE/TAE)	20,561
Alternative post-transplant mortality rates (increased)	26,744

Adapted with permission from BTG Ltd.[103]

Assessment Group critique of the BTG conventional transarterial therapy-eligible model

Downstaging and role of transplant in the UK

The company assumed that patients who are successfully downstaged become eligible for transplantation, and that no patients receive any other kind of curative therapy including resection or ablation. This was justified on the basis that few patients are expected to receive these other therapies. The company provided two sources in support of this assumption. In these studies, of the patients who received radical curative therapy after downstaging, the proportion who received resection ranged from approximately 5.9%[129] to 10%.[118]

Clinical advice received by the AG also suggested that at least a proportion of these patients would go on to receive resection rather than a transplant. This AG therefore considers the assumption that all patients will go on to receive a transplant to be unreasonable and likely to favour SIRT, as outcomes following resection have been demonstrated to be associated with poorer outcomes (recurrence and survival) than those following transplantation.[122] The relevance of downstaging to transplantation in UK practice is also unclear. Eligibility for transplantation in the UK has historically been defined by the Milan criteria,[130] and only recently has a service evaluation been introduced in which eligibility criteria have been expanded to permit downstaged patients to receive a transplant.[131,132] Furthermore, at the time of writing, this study has recruited only a small number of patients, and does not represent established national practice.

Modelling of pharmacological management

The progression status of patients in the pharmacological management health state was estimated as a 50 : 50 average of patients in the pre-progressed and post-progression states. This split is arbitrary and unlikely to accurately reflect the actual proportion of patients in each health state. A visual comparison of the PFS and OS extrapolation plots for sorafenib and BSC in the SHARP study[69] appears to show that a greater proportion of time is spent in the post-progressed health state. A more reasonable estimate of the ratio of patients in each group is likely to be 33 : 67. Furthermore, given that the PFS and OS plots for SHARP are available, time in state could have been explicitly modelled, avoiding the need for such an assumption. The implications of this assumption are important and may lead to overly pessimistic estimates for patients in this health state, as this split is used to estimate utility and cost of active treatment. Based on the 50 : 50 split assumed, this will tend to overestimate total QALYs as too many patients are assumed to be in the pre-progressed state, as well as overestimating costs associated with time on sorafenib, where treatment duration is linked to progression.

Exclusion of patients who received selective internal radiation therapy work-up procedure but not treatment with selective internal radiation therapy

An important omission from the economic analysis is the costs and outcomes associated with patients who receive work-up associated with SIRT but who subsequently do not receive SIRT. These costs should be included in the economic analysis because work-up costs will be incurred by the NHS if SIRT was to be implemented in practice. Furthermore, patients who fail the work-up procedure are likely to be different from those who go on to receive treatment, as demonstrated in the SARAH trial,[19] in which patients who failed work-up had significantly poorer outcomes than those who went on to receive SIRT. Excluding these patients from the analysis therefore underestimates total costs in the SIRT treatment arms and is likely to overestimate treatment benefits.

Modelling of comparator treatments

The company assumed equivalent efficacy between the SIRT treatments due to the paucity of comparative data, which the AG considered reasonable given the lack of data, and similarities in the treatment modalities. However, the BTG company submission[103] states that it considers this assumption to be conservative, and that it might be expected that TheraSphere would provide superior outcomes. The AG notes that no plausible clinical argument or clinical evidence was provided in support of this statement.

Downstaging outcomes

The key benefit of SIRT in this analysis was through the increased proportion of patients who achieved downstaging after treatment, which indirectly led to increased numbers of patients receiving curative therapy. The probability of downstaging was estimated using data from a study of TheraSphere and TACE patients.[29] The AG had concerns relating to the robustness and generalisability of this study. The study was retrospective and single centre, with non-randomised cohort arms, which could have left it open to confounding bias. Furthermore, the study retrospectively identified patients who were most likely to be downstaged to curative therapies and therefore the modelled population is not representative of the broad CTT-eligible population in the scope of the analysis, and predicts higher rates of downstaging than would otherwise be observed for this broader population.

There are also issues regarding the generalisability of the downstaging criteria applied in the Lewandowski *et al.*[118] study, which were based on tumour dimensions only. However, UK criteria, used in the UK service evaluation of downstaging, also take into account alpha-fetoprotein level.[131] This may mean that there are differences between these patients and those considered eligible for transplant in the NHS.

To estimate the transition of patients to the pre-transplant wait list, the observed probability of downstaging from the Lewandowski *et al.*[118] study was applied to the proportion of patients who remained in the 'watch and wait' health state, rather than being applied directly in the model. As a result, this method underestimated the proportion of patients who were downstaged: for TheraSphere, the model predicted that 48% patients were downstaged, compared with 58% reported by Lewandowski *et al.*,[118] and for TACE, the modelled versus observed proportion who were downstaged was 26% vs. 35%.

The company assumed that the mortality rate of patients in the 'watch and wait' health state was equivalent to that of the pre-transplant mortality rate, citing a lack of data to model this specific outcome. However, the Lewandowski *et al.*[118] study reported mortality rates that were censored to curative therapies, and it was unclear why these were not leveraged in the model. The same mortality rate was applied to both treatment arms, thereby assuming that the only impact of treatment on mortality is through the bridging of patients to transplant. Furthermore, the data used to estimate pre-transplant mortality was from a cohort of patients,[121] of whom only a proportion had HCC. The Lewandowski *et al.*[118] study also reported progression outcomes, which again were not used in the economic analysis.

The use of different sources for downstaging, progression and mortality outcomes also means that the evidence was derived from very different study populations, which led to a lack of internal consistency, and made it more difficult to validate the predictions of the model.

Transplant wait list outcomes

The data source used to estimate the time spent on the transplant wait list was estimated for a cohort of patients not specific to HCC. Patients on the transplant wait list are prioritised by their Model for End-Stage Liver Disease (MELD) score;[133] however, the presence of HCC adds 'exception points' to MELD, meaning that the wait list time is generally shorter for HCC patients. The AG obtained data from a report on the 1-year outcomes following the introduction of the National Liver Offering Scheme, which was implemented on 20 March 2018.[134] The median waiting time under the old offering scheme may not accurately reflect how long patients may wait under the new offering scheme. The median waiting time to transplant for HCC patients who received a transplant between 20 March 2018 and 19 March 2019 was 49.5 days, which is substantially lower than the value for the overall cohort.

The company provided an incomplete reference on the source of the data used to estimate the transition to pharmacological management, and so it was not possible to comment on the suitability of this source. In an interim report on a service evaluation of transplantation following downstaging of HCC patients in the UK,[132] of 27 patients enrolled in the programme to date, only one was removed from the wait list owing to the deterioration of their condition. This provides a much lower estimate of dropout than that estimated by the company, although the AG acknowledges that it is based on a smaller subset of patients.

The AG questions whether or not it is appropriate to apply the same transition probabilities and mortality rate to patients regardless of their initial treatment; however, the AG is not aware of any directly applicable evidence for a differential rate. There are many factors that determine the rate at which patients receive transplant; some of these will not be treatment dependent, including the availability of donor grafts, and some are dependent on treatment. Previous studies of SIRT and CTT with intent to downstage have demonstrated differential outcomes of transplantation and progression

between treatment arms; although these are based on very small patient numbers, there does appear to be a small benefit in favour of SIRT.[25,47] Although TheraSphere and TACE were given as downstaging rather than bridging therapies in the Lewandowski *et al.*[118] study and so are not directly applicable to outcomes for patients on the transplant wait list, OS censored to curative therapies was also significantly different between arms in favour of SIRT, particularly after 2 and 3 years. Similarly, the rate at which patients receive curative therapy following downstaging is also likely to differ between arms, as evidenced in the Lewandowski *et al.*[118] study. As such, the AG considers it unlikely that outcomes would be equivalent across different treatment modalities, although it is not possible to estimate directly without estimates of survival conditional on downstaging.

Pharmacological management

Outcomes for patients in the pharmacological management health state were based on the BSC arm of the SHARP trial;[69] the company stated that this was to avoid applying any benefit associated with a particular HCC treatment in the model, as patients modelled to receive pharmacological management would be given different treatments. This is not representative of patients in this health state, as a proportion of these patients would receive further active therapy, assumed by the company to be sorafenib. Because patients receiving sorafenib experience better outcomes than patients on BSC (as demonstrated by a HR of 0.69 for OS in SHARP[69]), this approach underestimates survival for patients in this health state. A more accurate approach would be to calculate outcomes separately for sorafenib and BSC and then weight according to the proportion of patients in the health state over time.

Furthermore, the SHARP trial[69] is unrepresentative of the patients who would receive BSC in this population for a number of reasons. Approximately 50% of patients in SHARP had extrahepatic spread, and would thus be contraindicated for SIRT treatment. A subgroup analysis of SHARP patients demonstrated that the sorafenib treatment effect was higher in patients with no extrahepatic spread (HR of 0.55 compared with 0.69 in the ITT population). Data from REFLECT,[12] which compared lenvatinib with sorafenib, also demonstrated that the prognosis for patients with extrahepatic spread is worse than for those without: in the ITT population, the median OS was 12.3 months, compared with 18.0 months in a population with no extrahepatic spread. In addition, the SHARP trial enrolled only patients who had not received previous treatment with systemic therapy, so BSC patients in SHARP do not represent the patients in the pharmacological management health state who previously received TACE or SIRT. The AG was advised that patients who present with HCC and are eligible for sorafenib are typically associated with a more rapidly progressing form of the disease and will have a higher mortality rate.

As a result, the cost-effectiveness analysis is biased in favour of SIRT through the selection of unrepresentative comparator data. The use of these data from SHARP[69] underestimates survival in the pharmacological management health state, thereby further inflating the relative treatment effect of SIRT, as fewer patients on SIRT than on other therapies enter this health state.

Post-transplant outcomes

The AG has concerns about the applicability of the sources used to estimate mortality following liver transplantation, and considers it uncertain whether or not the assumed treatment pathway is reflective of clinical practice.

The data set used to estimate long-term mortality after transplant is not specific to patients with HCC. Patients with HCC are at risk of tumour recurrence, which is linked to increased mortality.[122] This can be illustrated by a comparison of survival in the general liver transplant population and in a HCC population. The AG obtained a HCC-specific data set of survival outcomes for liver transplant recipients in the UK since 1994.[134] In this data set, patients with HCC (restricted to those aged > 60 years as a proxy for intermediate-HCC patients) had a 5-year survival of 71%. This was lower than for those in the general liver transplant data set, whose 5-year survival was estimated as 81%. Therefore, benefits estimated by the company model are likely to be overestimated.

By excluding tumour recurrences, the treatment pathway is also misrepresented by the model. Both the Bellavance *et al.*[122] and Lewandowski *et al.*[118] studies report on recurrences that occur after transplantation: approximately 20% of patients in the Lewandowski *et al.*[118] study and 14% of patients in the Bellavance *et al.*[122] study experienced recurrence after transplantation, with a 1-year relapse-free survival rate of between 73% and 89%. In addition, the AG found that, in its analysis of the HCC-specific transplant data set, > 10% of transplant recipients in the UK in this population experienced a recurrence in the first 5 years post transplant. The patients who experience a recurrence are at an elevated risk of death,[122] and these patients often experience a reduced quality of life and additional treatment-related costs.[135] By excluding recurrence after transplant, the model overestimates the QALYs and underestimates costs generated for transplant recipients, which biases the results in favour of the SIRT arm owing to a higher proportion of patients being downstaged.

Health-related quality of life

The total number of QALYs generated by the model is likely to be underestimated, owing to the source chosen and an error in how age-related disutility was applied.

Health state utility values were estimated from a range of sources, but were primarily based on the NICE appraisal of lenvatinib (TA551),[12] which enrolled patients with advanced HCC, of whom approximately 60% had extrahepatic spread. This population therefore had more advanced disease and does not reflect the model population of intermediate-HCC patients. Therefore, the utilities drawn from TA551[12] are likely to underestimate the quality of life for a CTT-eligible population, and disadvantages any treatment arm associated with increased life-years.

The AG considers the company to have incorrectly implemented age-related disutilities in the model, although the company contends that the application was appropriate. This 'error' has an impact on all health states, and results in patients experiencing much lower utilities than those observed in the cited sources. In the company's model, the decrement associated with ageing is estimated by estimating an absolute utility decrement for each health state relative to full health (i.e. 1 minus the reported health state utility) and then subtracting this decrement from the age- and gender-adjusted population norm from Kind *et al.*[127] For example, as patients enter the model at the age of 65 years, the age-adjusted utility started at 0.78, and the literature-derived absolute utility for 'watch and wait' patients was 0.75.[12] This meant that the age-adjusted utility for patients in the 'watch and wait' health state was 0.53 (0.78 – 0.25). The application of age-adjusted utilities in this way is inappropriate and ignores the fact that each health state utility is derived from an age-appropriate source, and thus already accounts for any age-related decline in HRQoL. Furthermore, this method is inconsistent with previous TAs[136–138] in which age-related disutilities have been applied, where age-related decrements are applied as a multiplier to health state utilities rather than as an absolute decrement.

Resource use estimates

Resource use was estimated in the model based on feedback from a single clinician at a centre in the UK that uses SIRT. As the company could not provide details of the questionnaire or transcript of the interview, it has not been possible to verify how these data were estimated. Therefore, there are a number of uncertainties regarding which treatment costs are included, such as AEs relating to subsequent therapy (sorafenib) or to transplant, or whether or not any bridging therapy was provided for patients on the transplant wait list.

The company's clinical expert advised that TACE and TAE patients had around three initial treatments in their respective arms, whereas patients in the DEB-TACE arm had an average of 1.5 initial treatments. As described in *Chapter 5*, *Sirtex submission: conventional transarterial therapy-eligible analysis*, there is apparent variation in the number of treatments that patients receive in practice, with values identified between 1.43 and 2.83 per patient for DEB-TACE and between 2.5 and 3.03 for TACE patients. The uncertainty in these numbers was not explored by the company. By implementing a single embolisation

cost for each CTT procedure, the company also did not explore any differences in the length of hospital stay between the different CTT treatments.

A proportion of patients in the pharmacological management health state receive sorafenib. This was estimated using data obtained from a survey of clinicians; as there were limited details provided on how the proportion was estimated, the underlying assumptions could not be validated. It appears that the cost of sorafenib was applied for the time that patients were in the pre-progression health state; however, this would overestimate the cost of treatment, because mean time on treatment with sorafenib is less than mean TTP.[11] The analysis also excludes patients who receive lenvatinib instead of sorafenib, and the proportion of patients who progress on sorafenib and receive subsequent treatment with regorafenib; clinical advisors to the AG suggest that this would be approximately 20% of patients.

The company assumed that the work-up procedure for each SIRT would be associated with the same resource use. This underestimates the costs for QuiremSpheres, as the use of QuiremScout is required and is associated with an additional procurement cost.

BTG submission: conventional transarterial therapy-ineligible analysis

The second model submitted by the company assessed the incremental cost-effectiveness of SIRT compared with systemic therapy for the treatment of HCC in patients ineligible for TACE. The SIRTs assessed in this analysis were TheraSphere, SIR-Spheres and QuiremSpheres. The systemic therapies assessed were sorafenib, lenvatinib and regorafenib. Clinical inputs in the model were drawn primarily from a NMA of comparative studies and a single-arm Phase 2 trial of TheraSphere.[139] The scope of the company's model is summarised in *Table 24*. The time horizon considered in the model is 20 years and adopts an NHS and PSS perspective in line with the NICE reference case. Costs and health benefits in the model were discounted at a rate of 3.5%. The price year used in the model was 2017/18. The BTG company submission[103] states that the model aimed to consider patients who are considered to have later-stage HCC, which the company defines as patients who either are ineligible for or have previously failed TACE.

TABLE 24 BTG model scope (CTT-ineligible population)

Model component	Description
Population	The patient population that is the focus of the cost-effectiveness analysis includes patients matching the following criteria: • People with later-stage disease who are ineligible to receive CTT
Intervention	SIRT: • TheraSphere • SIR-Spheres • QuiremSpheres
Comparators	Established clinical management without SIRT (including but not limited to target chemotherapy). The target chemotherapies are: • Sorafenib • Lenvatinib • Regorafenib
Analysis type	Cost-effectiveness (cost–utility) analysis
Economic outcome	Incremental cost per QALY gained
Perspective	NHS and PSS
Time horizon	20 years
Discount rate	Annual rate of 3.5% applied to costs and QALYs

Model structure

The model is a cohort-level partitioned survival model, which includes three health states: (1) progression free, (2) post progression and (3) dead. The model does not allow for downstaging to curative therapies. *Figure 12* presents an overview of the adopted model structure. The proportion of patients in each health state is determined as a function of the TTP and OS. The proportion of patients in the progression-free health state was based on the TTP curve, and the post-progression state was estimated as the difference between the OS and TTP curves. The proportion of patients in the dead state was determined by the OS curve.

For OS, the estimated treatment effect was drawn from a NMA of studies identified in the presented systematic review. This was then applied to parametric survival models fitted to KM data from a single-arm Phase II trial of TheraSphere.[139] A Weibull function was selected as the most appropriate survival model. TTP was modelled based on a naive comparison of relevant TTP data, and was assumed to follow an exponential survival function.

Health state utilities in the model are primarily determined by the presence or absence of disease progression, with values based on those used in TA551.[12] The model also separately accounts for loss of QALYs as a result of AEs. The model attempts to account for the impact of ageing by implementing an age adjustment factor; however, this was implemented incorrectly (see *Application of age-adjusted utilities* for further discussion).

The model includes the following resource costs: (1) procedural costs relating to the administration of SIRT, (2) drug acquisition and administration costs associated with systemic therapy, (3) monitoring and disease management costs, (4) costs associated with AEs and (5) palliative care costs.

The model employs the following structural assumptions:

- Health-related quality of life is determined according to the presence or absence of disease progression and the therapy received.
- Patients were not permitted to be downstaged to receive curative therapy; all patients were, therefore, assumed to receive palliative care.
- Time to progression for TheraSphere was modelled using an exponential function fitted to a single-arm study; comparator TTP was modelled based on median PFS extracted from trial and observational evidence identified as relevant by the company.
- Overall survival was modelled using a Weibull function fitted to a single-arm study of TheraSphere with a HR derived from a NMA to determine OS for other therapies.
- Adverse events are assumed to affect both costs and HRQoL.
- Palliative care costs are assumed to be incurred only during the final month of life.

Evidence used to inform the company's model

Overall survival

Overall survival for patients receiving TheraSphere was based on a single-arm Phase II trial of 52 patients with intermediate and advanced HCC.[139]

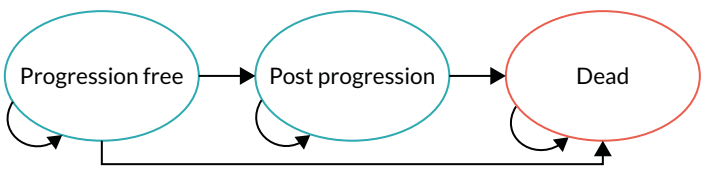

FIGURE 12 BTG CTT-ineligible model structure. Reproduced with permission from BTG Ltd.[103]

The following standard parametric survival models were fitted to the observed data: Weibull, log-normal, log-logistic, exponential and gamma functions. Assessment of the most appropriate parametric extrapolation was made with reference to statistical goodness of fit and clinical plausibility of survival estimates. The log-logistic and log-normal curves were eliminated on this basis, as they predicted that a small proportion of patients would not die within the time horizon of the model. The Weibull function was selected for the base-case analysis; no other extrapolations were explored in scenario analysis.

Estimation of OS for comparator therapies was based on a NMA of studies identified in the presented clinical effectiveness review. The NMA drew evidence from RCTs as well as non-comparative studies. The primary NMA reported better survival for TheraSphere than for sorafenib [HR (confidential information has been removed), 95% CrI (confidential information has been removed)], although this was not statistically significant.

Progression-free survival

Modelling of TTP for TheraSphere was implemented by fitting standard parametric functions to reported KM data from the same Phase II study used to model OS.[139] TTP was defined from first SIRT to first progression at any site. TTP, therefore, excluded mortality events, as the model only permits death following progression. As with OS, standard parametric curves were fitted to available KM data and the exponential function was selected as the most appropriate survival model based on the clinical plausibility of predicted outcomes. No other parametric functions were explored in the presented scenario analyses.

Owing to inconsistent reporting of TTP in the studies identified in the systematic review, a NMA for TTP was not feasible. Time-to-progression outcomes for comparator therapies were, therefore, based on a naive comparison, generated via median TTP and PFS data from relevant sources, which were converted to survival curves by assuming that TTP followed an exponential function. Median TTP for SIR-Spheres was based on a retrospective cohort study of patients who received SIR-Spheres,[45] with TTP assumed to be the same for QuiremSpheres owing to a lack of appropriate data. Median TTP for sorafenib was based on a weighted average of values reported in TA474,[11] TA551[12] and a retrospective cohort study.[45] Lenvatinib TTP was sourced from TA551,[12] and median TTP for regorafenib was sourced from TA555.[13] Note that all values sourced from TAs were based on PFS rather than TTP.

Health-related quality of life

The primary source of utility data used by BTG was TA551,[12] which drew evidence from the REFLECT trial[81] comparing lenvatinib with sorafenib, which collected EuroQol-5 Dimensions, three-level version (EQ-5D-3L), values from participants. The values used assume no differences in HRQoL between treatment arms, but do not attempt to account for differences in HRQoL as a result of AEs. This was carried out by applying a one-off utility decrement in the first cycle of the model, which was estimated by applying a 0.012 decrement per grade 3 or 4 event. Note that the BTG company submission[103] erroneously reports that a 0.014 decrement was applied in the model and miscalculates the decrement to be applied in the executable model.

In addition to the above, adjustments were also made to the health state utilities to account for the impact of ageing. This was undertaken by applying a decrement to every model cycle. The decrement applied was estimated by subtracting 1 from the age- and gender-adjusted population norm. Note that the BTG company submission[103] erroneously reports the decrements applied as 0.26 for the progression health state and 0.32 for the progressive disease health state, when the model applies a common decrement to both health states, which changes over time to reflect the increased age of the cohort. General population utility norms were sourced from Kind *et al.*[127] Utility values applied in the base-case analysis along with utility decrements are reported in *Appendix 15*, *Table 64*.

Selective internal radiation therapy procedure costs

See the review of the CTT-eligible population model (*Chapter 5*, *Evidence used to inform the company's model*) for details of SIRT procedure costs.

Drug acquisition costs: systemic therapies

Drug acquisition costs for sorafenib, lenvatinib and regorafenib were taken from the BNF.[115] Respective dosing was 800 mg, 12 mg and 160 mg per day. Dosing was based on recommended doses for HCC patients, described in their respective European Medicines Agency summary of product characteristics (SmPC). Duration of systemic therapy was based on progression, with patients assumed to continue systemic therapy until either progressive disease or death. *Appendix 15*, *Table 65*, summarises the drug acquisition costs applied in the model.

Subsequent treatments

A proportion of the patients receiving SIRT were assumed to receive sorafenib therapy following SIRT, with patients assumed to receive sorafenib after cycle 1 until disease progression or death. In the base-case analysis, the proportion of patients assumed to receive sorafenib was 33%, based on 'data on file'. Patients not receiving concomitant sorafenib were assumed to receive BSC. No subsequent therapies were modelled following disease progression in either model arm (SIRT or systemic therapy).

Health state costs

Resource use estimates were based on a survey of clinical experts conducted to inform resource use in TA189,[140] TA474[11] and TA551.[12] These included physician visits, laboratory and radiological tests, and hospital stays. Unit costs were derived from TA189,[140] and updated using *National Schedule of Reference Costs 2017–2018*.[107]

In addition to the above, a one-off cost was applied on treatment progression based on the costs applied in TA551.[124] This comprised additional laboratory and radiological tests (see *Appendix 15*, *Table 67*).

Total costs by health state are reported in *Appendix 15*, *Table 66*, along with a summary of one-off progression costs.

Adverse event costs

Unit costs associated with AEs were drawn from *National Schedule of Reference Costs 2017–2018*[107] and are summarised in *Appendix 15*, *Table 68*. No information or justification was presented with regard to how the specific costs used were selected.

Palliative care costs

The company's model includes a cost of £8191 to account for costs of palliation at the end of life. This was derived from a joint Nuffield Trust and Marie Curie report[128] into end-of-life cancer care and inflated to 2017/18 prices. This cost was applied on a patient's death and was applied for all modelled interventions.

Model results

The headline results presented in the BTG company submission[103] are based on the deterministic version of the model. Uncertainty surrounding model parameters was explored using scenario analysis and a PSA. The executable model also included a number of DSAs that were not presented in the company submission or appendices. The company's probabilistic results were estimated from 1000 Monte Carlo samples and were presented using CEACs and CEAFs only, with no ICERs from the probabilistic model in the company submission.

Table 25 presents the company's base-case estimates of cost-effectiveness using the corrected version of the model at the list price for sorafenib, lenvatinib and regorafenib. Based on the probabilistic version of the company's model, regorafenib was estimated to be the most cost-effective therapy.

TABLE 25 Summary of base-case results: BTG CTT-ineligible population

	Absolute		Incremental (relative to regorafenib)		
Treatment	QALYs	Costs (£)	QALYs	Costs (£)	ICER (£)
Probabilistic model (calculated by the Evidence Review Group)					
TheraSphere	0.681	49,574	0.185	12,778	69,070
QuiremSpheres	0.466	37,446	−0.030	650	Dominated
SIR-Spheres	0.465	37,406	−0.031	610	Dominated
Sorafenib	0.496	38,977	0.000	2181	Extendedly dominated
Lenvatinib	0.526	61,282	0.030	24,486	Dominated
Regorafenib	0.496	36,796			
Deterministic model					
TheraSphere	0.695	49,984	0.200	13,331	66,624
QuiremSpheres	0.470	37,496	−0.025	843	Dominated
SIR-Spheres	0.470	37,496	−0.025	843	Dominated
Sorafenib	0.500	39,059	0.005	2406	Extendedly dominated
Lenvatinib	0.530	62,647	0.035	25,995	Dominated
Regorafenib	0.495	36,653			

The results of the fully incremental analysis suggested that SIR-Spheres, QuiremSpheres and lenvatinib were dominated by one or more therapies, whereas sorafenib was extendedly dominated by TheraSphere. The estimated ICER for TheraSphere compared with regorafenib was £69,070 per QALY and estimated that TheraSphere generates an additional 0.185 QALYs at an additional cost of £12,778. The deterministic version of the model produces similar results, with an ICER relative to regorafenib of £66,624 per QALY.

Figure 13 presents the results of the DSA generated by the AG. The most influential parameters (of those assessed by the company) relate to the OS HR for regorafenib and the proportion of patients

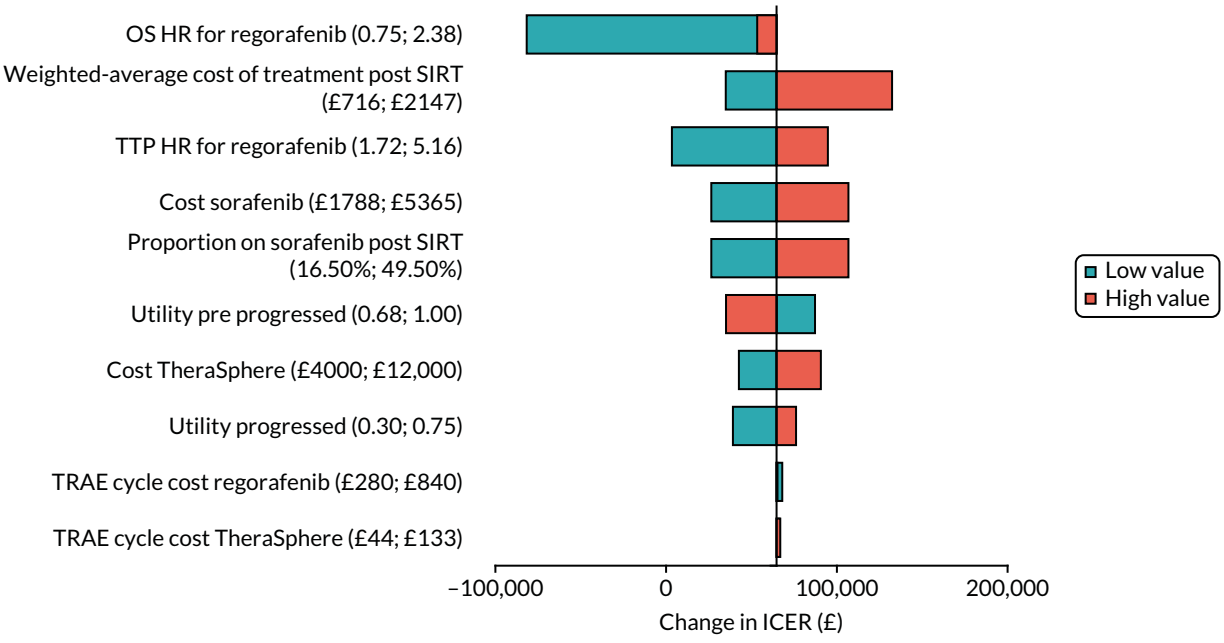

FIGURE 13 BTG DSA: tornado diagram. Reproduced with permission from BTG Ltd.[103]

assumed to go on to receive post-SIRT sorafenib. Additional scenario analysis presented by the company showed that the estimated ICER was influenced significantly by assumptions made about post-SIRT treatment. In the presented scenario analysis, in which no concomitant sorafenib was assumed, TheraSphere was estimated to be the most cost-effective intervention, with a deterministic ICER of £5870 per QALY.

The AG questioned the face validity of the utility values applied, and were concerned that the company had made a calculation error with respect to the calculation of the utility decrements. After clarification from the company, BTG confirmed that the utility decrements applied in the model were as intended by the company. See below for further critique of the utility values applied.

Critique of the BTG conventional transarterial therapy-ineligible model

Inappropriate inclusion of regorafenib as a comparator

The base-case analysis presented in the BTG economic analysis includes three systemic therapies: sorafenib, lenvatinib and regorafenib. The AG is of the view that regorafenib should not have been included as a comparator, as it is used only as a second-line therapy following sorafenib. This is stated in the SmPC for regorafenib and NICE's recommendation[13] for regorafenib, which restricts use to patients who have been previously treated with sorafenib.[141] The AG considers it entirely reasonable to model subsequent regorafenib use following sorafenib, but it should not have been directly compared with SIRT and the other systemic therapies.

Work-up without selective internal radiation therapy procedure

An important omission from the BTG economic analysis is the costs associated with patients who received work-up but did not continue on to the SIRT procedure. In the SARAH[19] and SIRveNIB[21] trials, 18.6% and 28.6% of patients, respectively, received work-up but did not continue on to receive SIRT. The AG considers the cost of patients who do not proceed to SIRT treatment important, as they constitute part of the incremental costs of implementing SIRT in the NHS. The AG further notes that many of these patients will receive other active therapies instead of SIRT, and it is therefore appropriate to model the associated costs and outcomes. For example, in the SARAH trial,[19] 62% of patients for whom work-up failed went on to receive sorafenib. The AG, therefore, considers that the costs associated with the administration of these alternatives should also be included in the economic analysis. The AG also notes that the clinical effectiveness data used to populate the model were based on the ITT population and, therefore, the clinical outcomes of these patients for whom work-up failed are implicitly included. This is inconsistent with BTG's stated position that only patients receiving therapy were considered.

Network meta-analysis and estimation of relative overall survival benefits

BTG conducted a NMA to compare TheraSphere with sorafenib for the treatment of unresectable HCC patients. Seven studies formed the primary network: two RCTs, one prospective study and four retrospective studies. There are differences in the studies included in the NMAs conducted by BTG and the AG. The BTG network included only studies conducted outside Asia, owing to known differences in both aetiology and treatment patterns in Asian populations. The AG identified additional studies that the company did not include or identify in its systematic literature review.[40] Unlike the AG, the company did not split the NMA into different populations of patients with differing stages of HCC disease. Therefore, the baseline BCLC stage, Child–Pugh status and the proportion of patients with PVT differed across studies. However, the population in the primary network was mostly advanced-stage HCC patients.

The validity of results from the NMA relies on the quality of the studies that make up the evidence base. However, there are considerable concerns regarding the quality of the prospective and retrospective studies. The prospective observational study by Woodall *et al.*,[37] comparing TheraSphere with BSC, which was excluded from the AG's NMA, presented significant baseline imbalances and evidence of selection

bias, as patients who failed to meet the pre-treatment TheraSphere requirements formed the 'no-treatment' arm. In addition, the retrospective studies[39,44,45] were all associated with a high risk of bias as there are significant baseline imbalances, unclear reporting of blinding and missing outcome data, and were excluded from the AG's primary NMA for these reasons.

Although the NMA reports better survival for TheraSphere than for sorafenib, this appears to be on the basis of the inclusion of a particular retrospective study, Biederman *et al.*,[39] which reports a very strong treatment effect on OS with TheraSphere compared with SIR-Spheres (HR 0.40, 95% CrI 0.20 to 0.78). As discussed in *Chapter 3*, *Risk of bias*, the four retrospective studies (including Biederman *et al.*[39]) and the prospective observational study are poor quality and were rated as being at a high risk of bias, which reduces the reliability of the NMA results.

Limited exploration of uncertainty surrounding survival functions

The BTG company submission[103] does not include any consideration of the uncertainty surrounding the range of potentially plausible survival functions for OS. Although a number of parametric functions were fitted to the available data for OS, the impact of alternative functions was not explored in the company's presented scenario analyses. Furthermore, there is no functionality in the presented executable model to implement alternative survival functions.

Omission of downstaging

The AG notes that the BTG economic model did not consider the possibility that patients may be downstaged to receive curative therapy. As stated in relation to the Sirtex CTT-ineligible model, the relevance of downstaging in an advanced-HCC population is unclear, with the AG's clinical experts suggesting that this would be a very rare occurrence in UK practice. However, downstaging was observed in a small number of patients in the SARAH trial[19] and, therefore, the potential benefits of downstaging represent an important uncertainty. Therefore, although the AG recognises that the inclusion of downstaging in the company's base case may be inappropriate, this uncertainty should have been explored in scenario analysis.

Modelling of progression-free survival

The BTG company submission states that it was not possible to obtain estimates of relative PFS from the NMA and, therefore, PFS was based on a naive comparison of reported estimates from studies identified as relevant by the company. The AG considers there to be a number of significant weaknesses in the company's approach, and that the selected median PFS for TheraSphere lacks face validity. Although the AG acknowledges that a NMA could not be run for PFS outcomes, based on the studies included in the company's network, the AG does not agree that a relevant network could not have been constructed (see *Chapter 4*). Importantly, as reported in *Chapters 3* and *4*, there are randomised comparisons of SIRT (SIR-Spheres) and systemic therapies (sorafenib) on which estimates of median PFS could have been based. The AG would consider such an approach preferable to the company's naive comparison, which used populations poorly matched with the modelled population. The AG further notes that this randomised evidence was ignored in favour of studies used in the relevant NICE appraisals, which focused on populations including a significant proportion of patients with extrahepatic spread, and, with respect to regorafenib, had already failed previous sorafenib therapy.

Further to the above, the AG also questions the plausibility of the modelled median PFS for TheraSphere. The modelled value of 11 months is 3.5 times longer than the value used for SIR-Spheres (3 months) and longer than the median OS reported in the SARAH trial[19] for both SIR-Spheres and sorafenib. Given the broad clinical similarity between TheraSphere and SIR-Spheres, and the lack of high-quality comparative evidence, the AG considers that it is unreasonable to assume such a large disparity in PFS.

Dosing and time on systemic therapy

Dosing of systemic therapies in the BTG economic analysis was based on the relevant SmPC, with a dose of 800 mg, 12 mg and 160 mg assumed for sorafenib, lenvatinib and regorafenib, respectively. These figures are likely to overestimate the dose received for all three drugs, as dose reductions and interruptions are common in patients receiving systemic therapy, and were observed in all relevant trial data. For example, the mean dose of sorafenib received in the SARAH trial[19] was 648 mg, not 800 mg. The company's model also does not account for the fact that the dosing of lenvatinib is weight dependent, with patients < 60 kg receiving 8 mg daily; 13% of patients in the Western subgroup of the REFLECT trial[81] weighed < 60 kg.

Time on systemic treatment in the BTG economic analysis is assumed to align with PFS. This is consistent with the SmPC for both sorafenib and lenvatinib, both of which indicate that therapy should continue for as long as clinical benefit is observed, or until toxicity becomes unacceptable. However, sorafenib, lenvatinib and regorafenib are all associated with significant tolerability issues, which means that many patients discontinue therapy prior to disease progression. This is seen in the pivotal trials, in which time on systemic therapy is always less than PFS. For example, median time on sorafenib in the SARAH trial[19] was 2.8 months, whereas median PFS was 3.7 months. Using PFS as an indicator of treatment discontinuation, therefore, may produce overestimates of time on treatment and consequently total drug acquisition costs for sorafenib, lenvatinib and regorafenib.

Subsequent therapy costs

The BTG economic analysis assumes that a proportion of patients receiving SIRT treatment (TheraSphere, SIR-Spheres or QuiremSpheres) move on to receive subsequent systemic therapy immediately following initial SIRT. These patients are assumed to continue therapy until disease progression. The AG considers the modelling of subsequent therapy in this way to be inconsistent with likely NHS practice and the supporting trial evidence, and that initiation of systemic therapy following SIRT would typically happen following disease progression. The AG acknowledges that, in the SARAH trial,[19] a proportion (11/52, 21%) of patients did receive subsequent systemic therapy prior to progression. However, there is no evidence to suggest that this was initiated immediately following SIRT; indeed, the SARAH[19] and SIRveNIB[21] trial protocols stipulated that further therapy should not commence until disease progression.

A further issue relating to the company's modelling of subsequent therapy is the assumption that patients receiving first-line sorafenib therapy will not receive further active therapy following progression. This is inconsistent with clinical practice, in which a proportion of patients will receive second-line regorafenib as per NICE's recommendations.[13] It is also not consistent with the modelled trial evidence, as a proportion of patients in the SARAH and SIRveNIB trials went on to receive subsequent therapy following discontinuation of sorafenib.

Application of age-adjusted utilities

Similar to the BTG economic analysis in the CTT-eligible population, the estimation of age-related disutility was implemented incorrectly, resulting in health state utilities being applied that are inconsistent with values used in previous TAs, as well as values reported in the SARAH trial.[19] For further details of this error, see *Chapter 5, Evidence used to inform the company's model.*

Further to the above, the AG considers age adjustment unnecessary in an advanced population in which the majority of patients die within 5 years; the application of age-adjusted utilities is unnecessary and not in keeping with norms for this type of model.

Calculation errors

A small number of calculation errors were identified and corrected as part of the AG's assessment of the BTG economic analysis. These errors related to:

- the estimation of the comparator TTP, which used an incorrectly estimated HR
- the calculation of per-cycle mortality and progression, which were estimated using a monthly cycle, whereas the rest of the model used a 4-week cycle.

These errors have only a marginal effect on the reported ICER, increasing the deterministic ICER from £64,693 to £66,624 per QALY.

Conclusions from the Assessment Group's assessment of the company's economic evidence

Conclusions from the company submissions provided by Sirtex and BTG are provided in the following sections. Please note that Terumo did not submit any economic evidence, and so a critique is not provided.

Sirtex submission: conventional transarterial therapy-eligible population

The Sirtex submission included a CMA of SIR-Spheres, TheraSphere, TACE and DEB-TACE in the CTT-eligible population. A cost–utility analysis was not undertaken for the CTT-eligible population owing to a lack of comparative evidence available for this group of patients. The CMA considered the costs of initial treatment, hospitalisation and management of AEs. The company presented a range of scenarios for the costs of each treatment option, using alternative sources and assumptions to provide a range of plausible costs. Rather than selecting a preferred scenario, the company noted that the range of costs associated with CTT, TheraSphere and SIR-Spheres overlapped, demonstrating the comparability of treatment costs.

The AG considered the presentation of a CMA for this population to be inappropriate and potentially misleading. Such an analysis is appropriate only if there is compelling and unambiguous evidence for equivalent efficacy between interventions. Results of the AG systematic review found very little high-quality evidence in this population, and the data identified were not sufficient to demonstrate clinical equivalence or a clinical difference between treatments. A focus on treatment costs only excludes possible important outcomes regarding people who are downstaged after treatment and become eligible to receive curative therapy, or receive subsequent therapy after progression of disease.

Sirtex submission: conventional transarterial therapy-ineligible population

The Sirtex submission also included a de novo model-based health economic evaluation of SIR-Spheres versus sorafenib in the restricted low tumour burden/ALBI 1 subgroup for CTT-ineligible patients. An economic analysis for the broader population of patients with intermediate or advanced HCC was also presented in scenario analysis. The company's model suggested that SIR-Spheres dominates sorafenib, producing more QALYs at a lower cost. The AG notes several concerns relating to the company's submitted model, in particular (1) the questionable relevance and validity of an analysis based on the low tumour burden/ALBI 1 subgroup, (2) the relevance and methods used to model the downstaging of patients to curative therapies, (3) the modelling of OS and in particular the use of data that was not censored for downstaging to curative therapy, (4) the questionable assumptions regarding the modelling of patients who underwent work-up but did not receive SIR-Spheres, (5) the number of SIRT treatments received, particularly the assumption that patients with bilobar tumours will have both lobes treated in one session, and (6) the duration of treatment on subsequent treatment.

Given the consistent direction of bias in the issues described in the sections above, the AG considers it probable that the incremental cost-effectiveness of SIR-Spheres compared with sorafenib is considerably higher than the estimates presented in the Sirtex company submission.[102]

BTG submission: conventional transarterial therapy-eligible population

For the CTT-eligible population, the BTG submission included a de novo model-based health economic evaluation of TheraSphere compared with two other SIRTs (SIR-Spheres and QuiremSpheres) and with TAE, TACE and DEB-TACE. The key benefit of SIRT assumed by this analysis was through the increased proportion of patients who achieved downstaging after treatment, which indirectly led to an increased number of patients receiving curative therapy. These outcomes were based on Lewandowski *et al.*,[29] a retrospective analysis of TheraSphere and TACE in patients identified as being candidates for downstaging. SIR-Spheres and QuiremSpheres were assumed to have equivalent efficacy to TheraSphere, and TAE and DEB-TACE were assumed to be equivalent to TACE.

The model estimated that the cheapest strategy was DEB-TACE, which dominated TAE and TACE. TheraSphere, QuiremSpheres and SIR-Spheres had a probabilistic ICER of £25,052 per QALY gained, compared with DEB-TACE.

The AG notes several concerns relating to the company's analysis, in particular (1) the relevance of downstaging to transplant in this population to UK clinical practice and the use of a non-HCC-specific data set to model outcomes in these patients, (2) the failure to properly account for patients who fail the work-up procedure and do not go on to receive SIRT, (3) the significant limitations in the clinical evidence used to model the relative effectiveness of TheraSphere with other therapies, (4) the inappropriate and incorrect implementation of age-adjusted utility values and (5) the inaccurate representation of patients in the pharmacological management health state. The net effect of these issues on the estimated ICER is unclear, as many issues work in opposing directions.

BTG submission: conventional transarterial therapy-ineligible population

For the CTT-ineligible population, the BTG submission included a de novo model-based health economic evaluation of TheraSphere compared with two other SIRTs (SIR-Spheres and QuiremSpheres) and three systemic therapies (sorafenib, lenvatinib and regorafenib). The corrected version of the company's submitted model suggests that the probabilistic ICER for TheraSphere versus regorafenib is approximately £64,513 per QALY gained.

The AG has several concerns relating to the company's submitted model, which serve to critically undermine the validity of the presented model. Many of these concerns were also present in the CTT-eligible model presented by BTG. These concerns include (1) the inclusion of regorafenib as a direct comparator at first-line when it is licensed only for use following sorafenib therapy, (2) the failure to properly account for patients who fail the work-up procedure and do not go on to receive SIRT, (3) the significant limitations in the clinical evidence used to model the relative effectiveness of TheraSphere with other therapies, (4) the inappropriate and incorrect implementation of age-adjusted utility values, (5) the questionable assumptions regarding the modelling of time on systemic therapies and (6) the assumptions made regarding subsequent therapies received following SIRT. As with the CTT-eligible model, the net effect of these issues on the estimated ICER is unclear, as many issues work in opposing directions.

Chapter 6 Independent economic assessment: scope of analysis

As described in *Chapter 2*, the scope of the systematic review conducted by the AG into the relative effectiveness of SIRT covered a broad population, which the AG split into three distinct populations based on the intent of treatment and the eligibility to receive CTTs. These three populations largely corresponded to early, intermediate and advanced HCC.

Assessment of the available clinical evidence to support an economic analysis in each of these three populations, however, revealed that much of the available evidence is from poor-quality observational studies, with only a very small number of high-quality randomised trials. These limitations in the availability of evidence have a number of important implications for the scope of the economic evaluation undertaken by the AG.

As described in *Chapter 3*, *Clinical effectiveness results*, only three studies were identified for the population with early HCC (patients who are eligible for transplant and CTT). The intent of treatment in this population is primarily to act as a bridge to transplantion and, therefore, to control disease so as to allow patients to remain within transplant criteria until a donor organ becomes available. The primary benefit of SIRT or CTT in this population would, therefore, be through its capacity to sustain a greater proportion of patients through to receiving a transplant. In this context, waiting time to transplant is of crucial importance, and is a determining factor in the proportion of patients who are ultimately likely to receive transplant. However, studies identified by the AG on bridging treatment efficacy were from a US setting, where waiting list residence times are significantly longer than in the UK: roughly 6–12 months in the USA,[25–28] compared with an average waiting time of approximately 50 days for HCC patients in the UK.[134] The relevance of the available data on bridging to transplant was therefore limited, and basing estimates of the relative proportion of patients successfully bridged to transplant in this context would provide potentially misleading estimates of the relative effectiveness of SIRT and CTT. Furthermore, in the UK, where wait times for transplant are relatively short, there is relatively limited scope for SIRT to offer significant health benefits and, therefore, it is unclear whether or not any additional costs associated with a SIRT procedure would be justified in this setting.

In the intermediate, CTT-eligible population, the evidence base was also considered too limited to inform a NMA (see *Chapter 3*, *Clinical effectiveness results*), with only one available randomised study providing comparative evidence on the effectiveness of SIRT with CTT. This RCT recruited 24 patients and compared SIR-Spheres with DEB-TACE.[23] In the intermediate-HCC population, the primary aim of therapy is to maintain locoregional control of the tumour to prevent progression to advanced disease, for which treatment options are more limited and survival outcomes are poor. There may also be a role for the use of locoregional therapy to downstage certain patients to make them eligible for potentially curative therapies such as liver transplant or resection. Key outcomes in this population are, therefore, TTP, as patient survival is largely dictated by progression to advanced disease, and the proportion of patients who are downstaged to curative therapy. However, the identified RCT[23] provided very limited data on TTP and PFS and did not report any downstaging events. Moreover, evidence on the relative effectiveness of alternative CTT was largely limited to survival outcomes. As a consequence, any economic analysis implemented in the CTT-eligible population would have had to rely on the Pitton *et al.*[23] RCT alone. A model based on this single small study would, however, have generated significant challenges in populating key clinical inputs, and it would not have permitted the model to address the potential role of downstaging in this population. Furthermore, any estimates of relative benefit would have been subject to very considerable uncertainty, meaning that the results of any model would have limited value for decision-making. The AG, therefore, considered it inappropriate to develop a full economic analysis in the CTT-eligible population. The AG notes that Sirtex reached a similar conclusion regarding the availability of evidence to inform a full economic analysis, and opted instead to present a

CMA. As outlined in *Chapter 5*, *Sirtex submission: conventional transarterial therapy-eligible analysis*, the AG considers the value of such an approach limited, as a CMA relies on the assumption of equal efficacy, for which there was not sufficient evidence.

In contrast with early and intermediate populations, the systematic review identified two large RCTs comparing SIR-Spheres with sorafenib in the advanced-HCC population.[19,21] The focus of the AG economic analysis is, therefore, on the CTT-ineligible population. Details of the AG's economic analysis are outlined in *Chapter 7*.

Chapter 7 Independent economic assessment: conventional transarterial therapy-ineligible population

A summary of the key features of the AG economic analysis for the CTT-ineligible population is presented in *Table 26*. The population covered by the AG base-case analysis is Child–Pugh class A patients, who are ineligible or who have failed CTT. Scenario analysis considers two further subgroups: (1) patients who have a low tumour burden and are ALBI 1 and (2) patients with MVI.

It should be noted that these analyses are limited in that they do not include all patients who are ineligible to receive or have failed CTT, as they do not cover Child–Pugh class B patients ineligible for CTT. In practice, these patients would be ineligible to receive systemic therapy as they are not covered by the relevant NICE recommendations and, therefore, in practice would receive BSC. The clinical evidence available comparing SIRT with BSC in an advanced-HCC population is, however, very limited, and as such it is not possible to extend the economic analysis to cover this population.

The interventions considered in the AG analysis were the three SIRTs (QuiremSpheres, SIR-Spheres and TheraSphere) and the comparators were the systemic therapies sorafenib and lenvatinib. Regorafenib was not included as a comparator in the AG's analysis as the NICE recommendation and SmPC for regorafenib in HCC permits use only in patients who have previously failed sorafenib therapy. Patients in the AG model are, however, permitted to move on to regorafenib following discontinuation of sorafenib.

TABLE 26 Summary of key features of the AG base-case model

Model component	Description

Population	The patient population that is the focus of the cost-effectiveness analysis includes patients matching the following criteria:
	• Patients with unresectable intermediate (BCLC stage B) or advanced (BCLC stage C) HCC
	  ○ For whom any conventional TAE therapies (TAE, TACE, DEB-TACE) are inappropriate
	  ○ With or without MVI
	  ○ Without extrahepatic disease

Intervention	SIRT: • SIR-Spheres yttrium-90 resin microspheres • TheraSphere yttrium-90 glass microspheres • QuiremSpheres holmium-166 PLLA microspheres
Comparator	Established clinical management without SIRT using the following targeted systemic therapies: • Sorafenib • Lenvatinib
Analysis type	Cost-effectiveness (cost–utility) analysis
Economic outcome	Incremental cost per QALY gained, incremental net monetary benefit
Perspective	NHS and PSS
Time horizon	Lifetime (10 years)
Discount rate	Annual rate of 3.5% applied to costs and QALYs

In all analyses, cost-effectiveness is evaluated in terms of the incremental cost per QALY gained over a lifetime time horizon from an NHS and PSS perspective. In line with the NICE reference,[142] case costs and health benefits were discounted at a rate of 3.5% per annum. Costs in the model were based on the 2017/18 price year.

Model structure

The structure of the AG model is presented in *Figure 14*. The AG model consists of a three-state partitioned survival model and decision tree for those intended to receive SIRT. Also presented is the structure of the downstaging scenario (see dashed lines), for which the outcomes of patients successfully downstaged to receive curative therapy are modelled separately. In the AG model, those allocated to receive SIRT enter a decision tree representing the work-up procedure. A proportion of these patients go on to receive SIRT following work-up, whereas others are not considered suitable for SIRT or otherwise withdraw consent, so can go on to receive either BSC or a systemic therapy. In the AG base case, patients then move into the main partitioned survival model.

The proportion of patients who receive work-up in the AG base case is based on the SARAH trial,[19] from which efficacy outcomes for these patients are drawn. Of the 226 patients who underwent work-up, 42 (18.6%) did not receive SIRT. Two further scenarios are presented in *Scenario analyses*, which explore the effect of using the lower and upper bounds of work-up 'failure' identified in the literature (5%[143] to 28.6%[21]).

The model uses a lifetime (10-year) time horizon (< 0.1% of patients alive at 10 years in the most optimistic scenario), and takes an NHS and PSS perspective. Costs and health outcomes are discounted at a rate of 3.5% per annum, with cost-effectiveness expressed in terms of the incremental cost per QALY gained and incremental net monetary benefit (NMB). Costs were valued at 2017/18 prices.

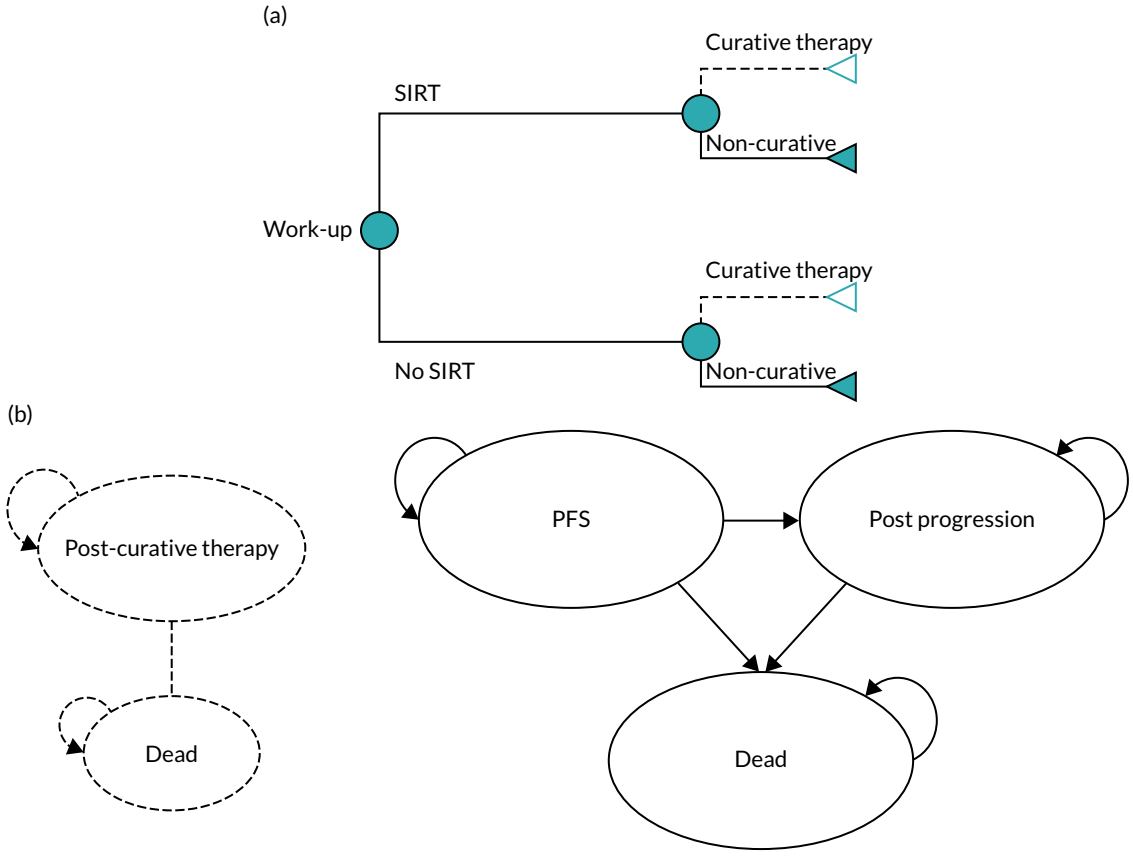

FIGURE 14 Overview of the CTT-ineligible population AG model structure (with dashed curative therapy scenario). (a) Work-up outcome decision tree; and (b) post-SIRT Markov model.

As shown in *Figure 14*, the structure of the partitioned survival model is broadly similar to that adopted within both the BTG and Sirtex models (see *Chapter 5*, *Review of economic evidence submitted by companies*), consisting of three health states: (1) progression free, (2) post progression and (3) dead. For any time, t, the probability that a patient is alive and progression free is given by the cumulative survival probability for PFS, whereas the probability that a patient is alive is given by the cumulative survival probability for OS. The probability that a patient is in the post-progression state at any time, t, is given by the difference between the cumulative survival probabilities for PFS and OS. Health and cost outcomes from the partitioned survival models for each intervention were multiplied by the proportion of patients who received each within the particular treatment arm as per the decision tree.

As with the Sirtex model, HRQoL is defined according to the presence or absence of disease progression as well as treatment received. The model includes costs associated with SIRT procedures (work-up costs, acquisition costs and procedure costs), drug acquisition, health-state costs (consultant-led outpatient visits, nurse-led outpatient visits, electrocardiography, blood tests and CT scans), costs associated with managing grade 3 or 4 AEs, BSC-related costs (consultant-led outpatient visits, CT scans, MRI scans, specialist palliative care visits and palliative radiotherapy) and end-of-life care costs.

Model input parameters

A summary of the data sources used to populate the AG's base-case model is presented in *Table 27*. These are discussed in greater depth over the following sections.

Treatment effectiveness

The base-case analysis used data from the SARAH,[19] SIRveNIB[21] and REFLECT trials.[81] Scenario analyses also drew on a number of observational comparisons of SIR-Spheres and TheraSphere (see *Chapter 4*, *Network 3: adults with unresectable hepatocellular carcinoma who are ineligible for conventional transarterial therapies*, for details).

The comparison of SIR-Spheres with sorafenib was based on pooled data from the SARAH and SIRveNIB trials. Modelled data from SARAH were supplied by Sirtex for both PFS and OS, and data were extracted from published literature sources from SIRveNIB.

The source of modelled survival data from the SARAH and SIRveNIB trials differed according to therapy received. For patients receiving sorafenib, OS and PFS outcomes were based on the ITT populations (sorafenib, $n = 400$), whereas OS and PFS outcomes for patients receiving SIR-Spheres are modelled based on the per-protocol population of each trial (SIR-Spheres, $n = 304$). This is done to account for the proportion of patients who fail the SIRT work-up procedure, and subsequently do not undergo the main SIRT procedure. The outcomes of patients who fail the work-up procedure are modelled independently, and are based on near-complete KM data from the SARAH trial (work-up failures, $n = 42$). The proportion of patients failing the work-up procedure is based on the SARAH trial. The DSA included a range of estimates for work-up failure, based on the number of work-up failures reported in SARAH and SIRveNIB and other estimates provided by Sirtex. To avoid the double-counting of patients who are downstaged to receive curative therapies, the data included from SARAH, for both SIR-Spheres and sorafenib, are censored for downstaging. There was no downstaging reported in the SIRveNIB trial publication[21] and no patients received subsequent therapies that could be considered 'curative', so it was assumed that no patients were downstaged to receive curative therapies in these data.

The comparative effectiveness of lenvatinib was drawn from the NMA presented in *Chapter 4*, *Results*. The HR for lenvatinib versus sorafenib was applied to the Weibull curve fitted to the sorafenib data drawn from the SARAH and SIRveNIB trials. Proportional hazards is, therefore, assumed between sorafenib and lenvatinib.

TABLE 27 Summary of sources of input parameters in the AG base-case economic model

Model parameter	Evidence source
OS	Parametric survival models fitted to pooled OS data from the SARAH[19] and SIRveNIB[21] trials for both SIR-spheres (per protocol) and sorafenib (ITT). A HR from the AG's NMA was applied to the sorafenib OS curve to estimate OS for lenvatinib. The OS for patients who received work-up but were ineligible to receive SIRT was modelled using the observed KM data from SARAH[19]
PFS	Parametric survival models fitted to pooled PFS data from the SARAH[19] and SIRveNIB[21] trials for both SIR-spheres and sorafenib. A HR from the AG's NMA was applied to the sorafenib PFS curve to estimate OS for lenvatinib
Health state utilities	Utilities were generated by Sirtex from SARAH trial[19] data, and were applied by treatment class (SIRT/systemic therapy) Pre progression: EORTC QLQ-C30 scores taken from the post hoc analyses of the SARAH trial[19] for the per-protocol population were mapped to EQ-5D using a mapping algorithm developed by Longworth *et al.*[113] Post progression: EORTC QLQ-C30 scores taken from the post hoc analyses of the SARAH trial[19] for the per-protocol population were mapped to EQ-5D using the algorithm developed by Longworth *et al.*[113]
Proportion receiving SIRT	The proportion receiving SIRT after work-up was based on the full SARAH trial[19] population. Number of administrations of SIRT was based on the SARAH trial[19]
SIRT costs	Acquisition cost: Sirtex company submission,[102] BTG company submission[103] and Terumo company submission[104] Work-up costs: BTG-elicited values from The Christie NHS Foundation Trust (personal communication) Procedure costs: *National Schedule of Reference Costs 2017–2018*[107]
Systemic therapies costs	Sorafenib and lenvatinib: BNF[115] Dosing of sorafenib: SARAH trial[19] Dosing of lenvatinib: REFLECT[81] Western subgroup Duration of sorafenib: SARAH trial[19] Duration of lenvatinib: PFS HR from REFLECT.[81] Applied to SARAH,[19] sorafenib time on treatment
Subsequent treatment costs	BNF,[115] eMIT[116] and TA555 (regorafenib)[13]
AE costs	AEs experienced by ≥ 5% of the population were modelled, with rates drawn from the SARAH[19] and REFLECT[81] trials. Costs were drawn from *National Schedule of Reference Costs 2017–2018*,[107] with cost categories based on NICE TA474[11] and 551[12]
Health state costs	Sirtex survey of clinical experts and *National Schedule of Reference Costs 2017–2018*[107]

In the AG's base-case analysis, equivalence is assumed between the SIRTs owing to a lack of randomised evidence on the relative effectiveness of each SIRT. An exploratory scenario analysis is also presented in which the effectiveness of TheraSphere was based on two non-randomised comparative studies[39,40] (SIR-Spheres, $n = 34$; TheraSphere, $n = 78$), with a HR versus SIR-Spheres drawn from the NMA. In this scenario, the HR is applied to the modelled parametric functions fitted to the pooled SIR-Spheres data and, therefore, proportional hazards is assumed for this comparison (see *Extrapolation of progression-free survival and overall survival evidence* for consideration of the plausibility of this assumption).

In addition to the base-case analysis in which the modelled population was based on pooled analysis of the SARAH and SIRveNIB trials, additional scenario analysis was implemented in a number of alternative populations. To account for uncertainties in the relevance of the Asia-Pacific population to

UK practice, a scenario was implemented using data only from the SARAH trial. Two further subgroup analyses based on the SARAH trial were also considered: the restricted low-tumour burden and ALBI 1 subgroup (SIR-Spheres, $n = 28$; sorafenib, $n = 44$), and patients with MVI (SIR-Spheres, $n = 64$; sorafenib, $n = 81$). In both subgroup analyses, the comparison between SIR-Spheres and sorafenib is made using data drawn from the relevant subgroup of the SARAH trial only. Appropriate IPD were requested by the AG for these subgroups of the SIRveNIB trial but Sirtex had only limited access to the IPD from the SIRveNIB trial and did not have subgroup data from all enrolling centres. Subgroup data were not available to support the comparative effectiveness of lenvatinib and TheraSphere. This scenario, therefore, uses only data for SIR-Spheres and sorafenib, assuming equivalent efficacy across SIRTs and between lenvatinib and sorafenib.

Extrapolation of overall survival and progression-free survival evidence

For each data set, model selection was conducted in line with the process described in the NICE DSU Technical Support Document 14.[117] To assess the appropriateness of alternative parametric models, log-cumulative hazard plots were produced to illustrate and assess the hazards observed in the trial. Curve fitting was conducted using the 'survival' and 'flexsurv' packages in R (The R Foundation for Statistical Computing, Vienna, Austria). Exponential, Weibull, Gompertz, log-normal, log-logistic, gamma and generalised gamma models were considered.

The AIC and BIC fit statistics were examined to assess the comparative internal validity of competing models. The final choice of models for the economic analysis was made on the basis of fit to the observed data as well as consideration of the clinical plausibility of candidate models.

Overall survival

The analysis of OS for the base-case analysis was based on time-to-event data from the SARAH trial supplied by Sirtex, and KM curves from the SIRveNIB trial.[21] Pooled KM curves for the base-case population are presented in *Appendix 16*, *Figures 26* and *27*. Survival estimates can be found in *Appendix 16*, *Table 71*.

Standard parametric survival functions were fitted to the survival data available for each of the considered populations, and log-cumulative hazard plots were generated to assess any changes in hazards over time (see *Appendix 16*, *Figure 28*). Plots of each of the fitted parametric models with the observed KM OS curves are presented in *Figures 15* (SIR-Spheres) and *16* (sorafenib). Model fit

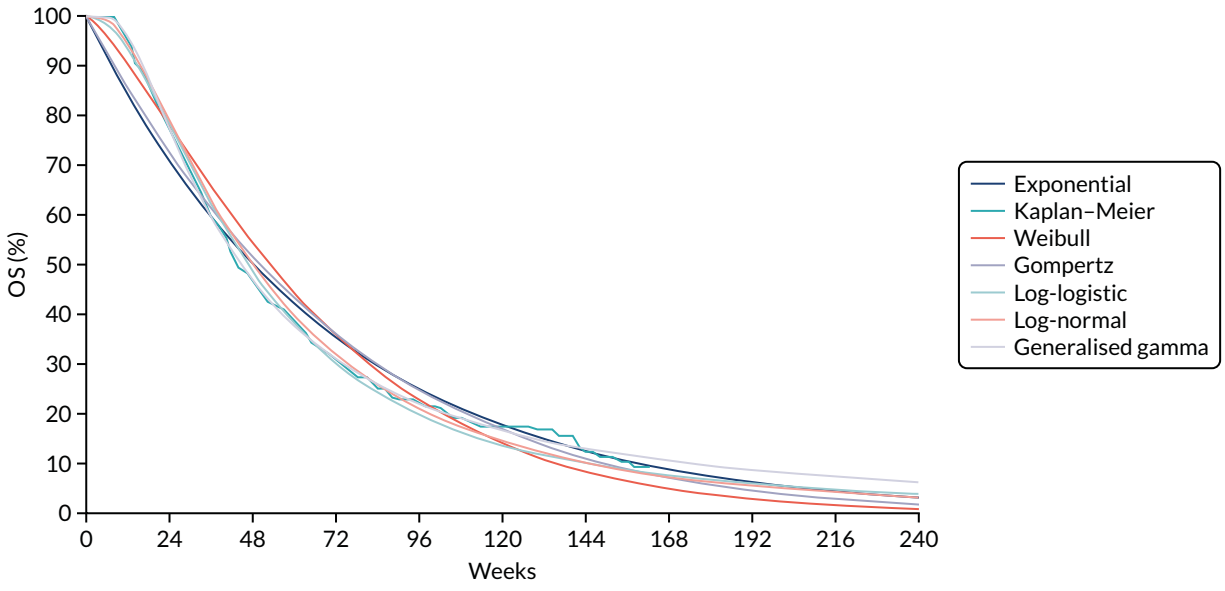

FIGURE 15 Extrapolation of OS: SIR-Spheres.

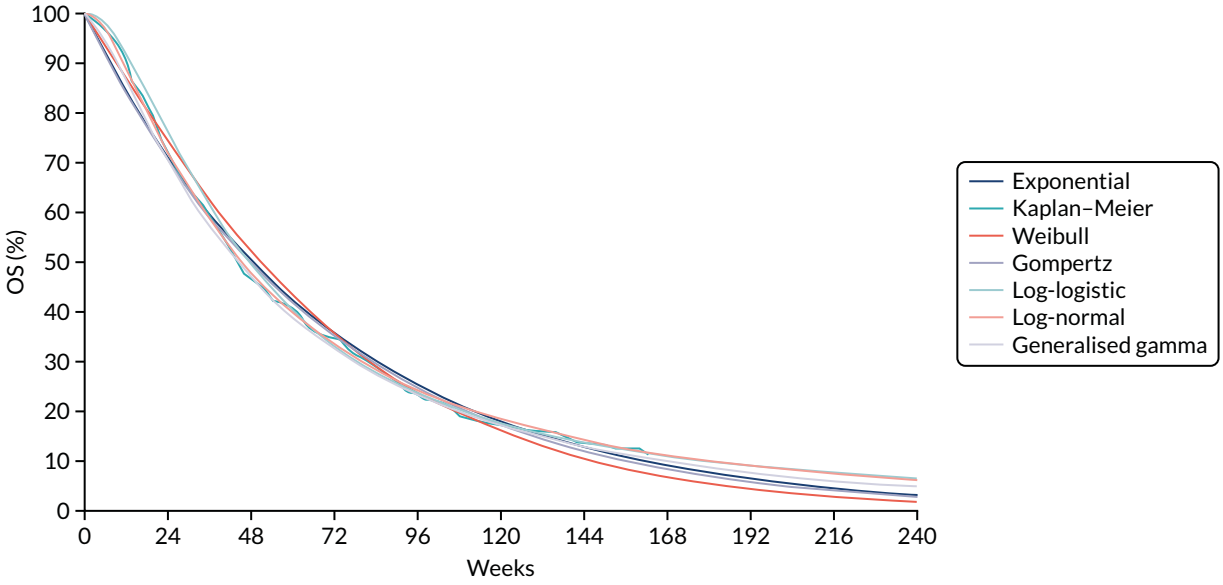

FIGURE 16 Extrapolation of OS: sorafenib.

statistics are summarised in *Appendix 16*, *Table 72*, which showed that the generalised gamma model had the best fit, with the log-normal and log-logistic curves also having similar statistical fit, thereby providing little justification to discriminate between these models on this basis of fit statistics. The generalised gamma, log-normal and log-logistic models are, however, all accelerated failure time models and, as such, a HR cannot be applied to estimate outcomes for lenvatinib patients, and would likewise not permit scenarios in which differential outcomes are assumed for TheraSphere, which would similarly require the application of a HR. To accommodate the use of HRs, the AG base-case analysis, therefore, selected the Weibull function, which has the best statistical fit from the remaining curves, and was considered the most clinically plausible. The AG considered this reasonable given the limited data to accommodate accelerated failure time functions and the small variation in predicted incremental survival across all six functions, but acknowledges this as a limitation of the presented base-case analysis. Scenario analysis is, therefore, presented, in which the generalised gamma, log-normal and log-logistic functions are used to model OS. In these scenarios, equivalence is assumed between sorafenib and lenvatinib.

For scenarios run on the SARAH trial[19] subpopulations described previously, the Weibull function was retained to model OS outcomes. Fit statistics for the SARAH trial whole population, low tumour burden/ALBI 1 subgroup and no-MVI subgroup are reported in *Appendix 16*, *Table 74*. Plots of each of the fitted parametric models with the observed KM OS curves are presented in *Appendix 16*, *Figures 30* and *31* (SIR-Spheres) and *Figures 32* and *33* (sorafenib). In all three scenarios, the Weibull function had a good statistical and visual fit to the observed data.

Progression-free survival

The analysis of PFS for the base-case analysis was based on supplied time-to-event data from the SARAH trial[19] and KM curves from the SIRveNIB trial.[21]

Similar to the approach previously described for OS, standard parametric survival functions were fitted to the survival data available for each of the considered populations (*Figures 17* and *18*), and log-cumulative hazard plots generated to consider the change in hazards over time (see *Appendix 16*, *Figure 29*). Plots of each of the fitted parametric models with the observed KM OS curves are presented in *Appendix 16*, *Figures 34* and *35* (SIR-Spheres) and *Figures 36* and *37* (sorafenib). Similar to OS, model fit statistics for the generalised gamma, log-normal and log-logistic functions were superior to other functions (see *Appendix 16*, *Table 73*). These functions were, however, rejected to accommodate the application of a HR for lenvatinib

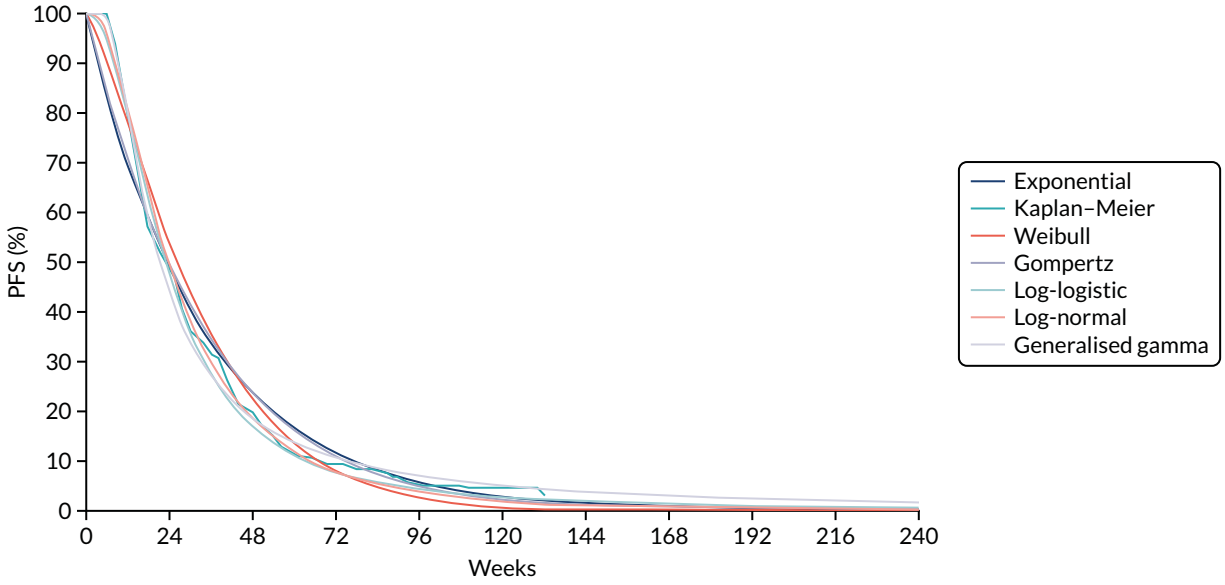

FIGURE 17 Extrapolation of PFS: SIR-Spheres.

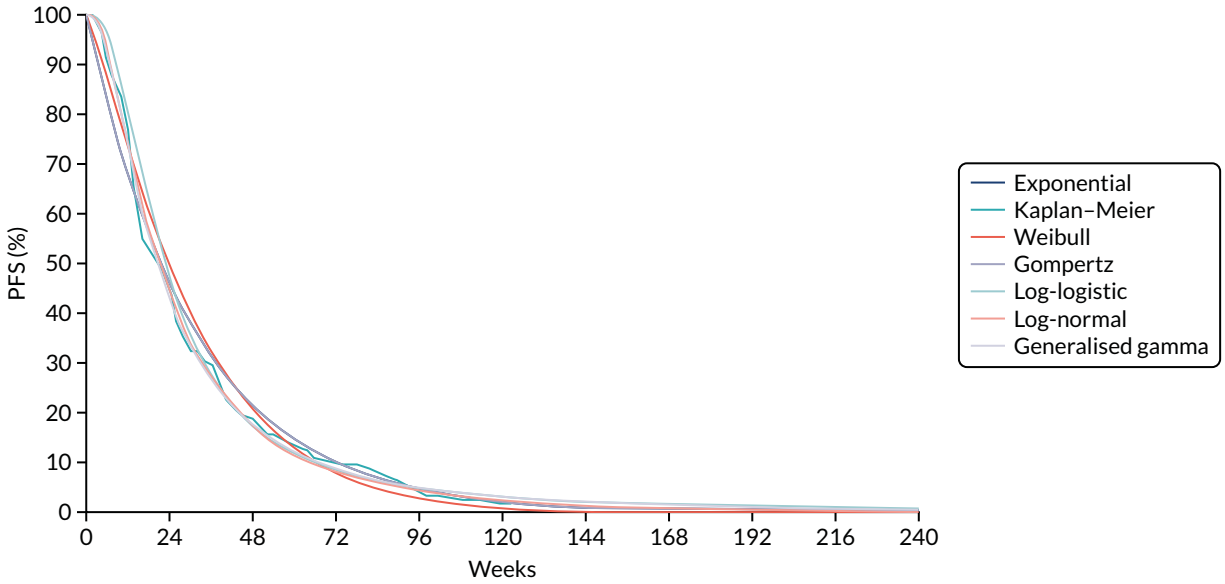

FIGURE 18 Extrapolation of PFS: sorafenib.

and the implementation of scenarios assuming differential effectiveness for TheraSphere. The Weibull function was, therefore, selected in the AG base-case analysis as this had the best statistical and visual fit to the observed data and was considered clinically plausible.

Overall survival for patients downstaged to curative therapy

The base-case analysis does not allow for downstaging to curative therapies, owing to uncertainties over whether or not this is realistic in a population of patients with advanced disease. A number of scenarios are presented in which downstaging is allowed for. The proportion of patients downstaged is based on the values reported in the SARAH trial[19] and varied depending on the efficacy subgroup used (see *Appendix 16*, *Table 69*). Outcomes for patients downstaged to curative therapy were based on a US prospective cohort study,[112] which recruited 267 patients with HCC, including 191 with intermediate and advanced disease. This study compared outcomes for patients who had received palliative care with those who received potentially curative therapies (liver transplantation, surgical

resection or tumour ablation). Using Cox multivariate proportional hazards, the HR for OS with potentially curative treatments versus non-curative treatment was 0.29 (95% CI 0.18 to 0.47). This HR was applied to the pooled sorafenib ITT arms of the SARAH and SIRveNIB trials in all scenarios. This was carried out to prevent the outcomes of downstaged patients varying depending on the patient population selected or by treatment arm; advice from clinical advisors to the AG suggested that outcomes post-curative therapy would be similar regardless of patient characteristics or treatment received to achieve downstaging. The sorafenib ITT arm was used as this was considered to best match care received in the analysed patient cohort, and is most representative of the current standard of care in UK practice.

Adverse event rates

The probability of experiencing grade 3 or 4 AEs for SIR-Spheres and sorafenib was taken directly from the per-protocol population of the SARAH trial.[19] Based on clinical advice received by the AG, AE rates for TheraSphere and QuiremSpheres were assumed to be the same as for SIR-Spheres. AE rates for lenvatinib were drawn from the REFLECT trial.[81] See *Appendix 16*, *Table 70*, for rates applied.

Health-related quality of life

Literature review and mapping of health-related quality-of-life estimates

A targeted review of published studies reporting utility estimates for patients with HCC or cirrhosis was undertaken to supplement data extracted from studies on SIRT and its comparators. Details of the search strategy used are described in *Appendix 3*. The objective of these searches was to identify health state utilities of patient populations that may not have been captured in studies included in the main systematic reviews. The required utilities included:

- decompensated cirrhosis (any cause)
- post-CTT disutility
- post-resection disutility
- pre- and post-transplant utilities.

The identified studies recorded HRQoL using a number of tools, namely Short Form questionnaire-36 items (SF-36) and EORTC QLQ-C30. NICE prefers the use of generic preference-based measures (i.e. EQ-5D) for the calculation of health state utilities. Therefore, mapping algorithms typically based on multinomial regression model coefficients can be used to transform disease-specific measures of health status into a EQ-5D-based utility score. Domain scores for relevant populations were mapped onto EQ-5D using the two-part beta model as developed by Woodcock and Doble[144] for EORTC QLQ-C30 scores, and a model developed by Rowen *et al.*[145] was used to transform SF-36 outcomes.

Modelled health state utilities

The AG's base-case model for CTT-ineligible patients applies different health state utilities based on the type of therapy received to reflect any differences in their respective AE burdens. Because utilities were drawn from patients in the SARAH trial, disutilities associated with type and length of any AEs were assumed to have been captured, and thus were not considered separately. In the absence of any evidence suggestive of a difference in HRQoL between the three SIRTs, the AG has assumed that patients experience the same quality of life regardless of whether they received SIR-Spheres, TheraSphere or QuiremSpheres. Likewise, the HRQoL estimates associated with the systemic therapies, namely sorafenib and lenvatinib, are assumed to be the same as one another, but marginally lower than those applied to SIRT, as observed in the SARAH trial[19] (see *Table 28*). An additional scenario in which health state utilities from the lenvatinib technology appraisal are applied is presented in *Scenario analyses*.

Age-related disutilities

Age-adjusted UK population norms from Szende *et al.*[146] were applied to the utility values included in the model. Age-related decrements were estimated in the form of a multiplier, with decrements applied relative to the populations on entering the model. This allows for the trial-derived utilities applied in the model to account for age-related decline in HRQoL as the population ages over time.

Selective internal radiation therapy health state utilities

The health state utilities associated with SIRT in the CTT-ineligible model were based on the per-protocol subgroup of the SARAH trial as calculated by Sirtex in its evidence submission (see *Chapter 5*, *Evidence used to inform the company's model*, for details). EORTC QLQ-C30 summary scores were mapped to EQ-5D using the algorithm developed by Longworth *et al.*,[113] and utilities were calculated based on UK general population weights.

The per-protocol utilities were considered to better reflect the HRQoL associated with SIRT than those derived from the ITT population, as 22.4% of patients randomised to SIRT did not receive SIRT in the SARAH trial. These patients may have received other systemic therapies or BSC, or were otherwise too unwell to receive SIRT; thus, the ITT utility values may not have represented those of a SIRT-treated population. There were no further utility decrements applied to these utilities as these are likely to have been captured in the SARAH trial results. The health state utilities applied in the model are presented in *Table 28*.

Systemic therapy health state utilities

Health state utilities applied to modelled patients receiving the systemic therapies sorafenib and lenvatinib were taken from the per-protocol subgroup of sorafenib patients in the SARAH trial.[19] The difference in utility between SIRT and sorafenib in this subgroup was 0.011, which the AG considered to account sufficiently for the ostensibly greater burden of AEs associated with these drugs. Utilities applied to patients who received work-up but ultimately did not receive SIRT were weighted by the proportion on systemic therapy versus BSC (61.9% and 38.1%, respectively). This assumes that patients not on systemic therapy had a utility equivalent to those on SIRT, which may overestimate the HRQoL of BSC patients, as a proportion were likely to have been too unwell to receive systemic therapy.

Post-transplant health state utilities

The AG scenarios 6 and 10 include the possibility for downstaging; therefore, post-transplant utilities were considered for use in the model. Pre-transplant health state utilities are assumed to be equal to those experienced in pre-progression for SIRT, systemic therapies and BSC. Post-transplant health state utilities are assumed to be equal to those experienced on SIRT, regardless of which treatment a patient received before downstaging to transplant. However, it is likely that patients who received a transplant may have a better HRQoL than the per-protocol population of the SARAH trial.

Despite multiple studies showing that recipients of liver transplant enjoy increased HRQoL post transplant in comparison with pre transplant,[113,147–149] a lack of generalisability between these studies

TABLE 28 Health state utilities included in the AG CTT-ineligible model

	Utility		
Health state	**SIRT**	**Systemic therapy**	**Work-up: no SIRT**
PFS	0.710	0.699	0.703
Progressive disease	0.668	0.657	0.661
Post transplant[a]	0.710	0.710	0.710

a AG scenarios 6 and 10 only.

and the population included in the model renders the absolute utility values reported in the literature too uncertain for inclusion. Studies also show that HRQoL remains lower for liver transplant recipients than for healthy patient controls.[150–152] However, as with the pre- and post-transplant utilities, there is insufficient evidence to suggest that these studies are generalisable to the modelled population. Given the lack of evidence to definitively suggest that utility values in the post-transplant HCC population are lower than in the general population, the AG believes that the utility values observed in the general population represent the upper bound of the utility expected in the post-transplant population.

Sources of resource utilisation and cost data

A targeted review of published studies reporting resource use and cost data for patients with HCC or cirrhosis was undertaken. Details of the search strategy used are described in *Appendix 4*. This review, however, identified little in the way of published literature. Resource use and cost inputs used in the AG's economic model were, therefore, derived primarily from targeted literature searches, previous NICE technology appraisals and the estimates presented in the companies' evidence submissions for the present appraisal. Overall costs are determined by treatment costs (acquisition, procedures and monitoring), changes in health service utilisation driven by disease status (i.e. progression free, progressed disease and death) and AE management. The assumptions applied to each category are discussed in the following sections. Note that confidential Patient Access Scheme (PAS) discounts are available but not included here for QuiremScout, sorafenib, lenvatinib and regorafenib. Please refer to *Appendix 17* for results including all PAS discounts. A summary of the AG model cost inputs is presented in *Summary of Assessment Group base-case analysis inputs and assumptions*.

Treatment costs and resource use

Work-up costs and number of procedures

Patients allocated to receive SIRT must first undergo a work-up procedure to assess their suitability for treatment with SIRT, and to plan the procedure through angiographic evaluation and occlusion of any vessels that could carry microspheres away from the liver to the gut. Although work-up is a one-off procedure, those patients who required a second SIRT procedure owing to an unsuccessful or incomplete first procedure are likely to need a second work-up.

In the SARAH trial,[19] 17 of the 184 patients who received SIRT required re-treatment owing to an unsuccessful or incomplete first procedure (nine received a second work-up but were not re-treated). Therefore, patients who received any of the SIRTs incurred the cost of 1.09 work-up procedures to account for re-treatment. As the model independently considered the costs and outcomes for patients who underwent work-up but ultimately did not receive SIRT, these individuals were assumed to receive 1.0 work-up procedures. The AG's base case assumed that 18.6% of patients who underwent work-up did not go on to receive SIRT in line with the SARAH trial[19] data. However, in recognition of the uncertainty around this value, a number of alternative scenarios are presented in *Sensitivity analyses results*.

Work-up costs used in the AG base case were based on the values BTG elicited from The Christie NHS Foundation Trust (see *Appendix 15*, *Table 60*). The largest expenditures were staff costs and SPECT/CT. The total cost of a single work-up procedure for SIR-Spheres and TheraSphere used in the AG model was £860.32, and the work-up cost of £5178.32 for QuiremSpheres comprised the list price of QuiremScout and the BTG-elicited value excluding the £74 cost of the technetium-99m MAA agent. This does not include the PAS discount available for QuiremScout.

Selective internal radiation therapy treatment costs and number of procedures

Patients in the AG model received an average of 1.21 SIRT procedures. This is based on the assumption that patients requiring bilobar treatment will require two separate SIRT procedures, separated by a few weeks (as per the SARAH protocol[153]), and that patients will be re-treated owing to an incomplete or unsuccessful first treatment. The clinical advisors to the AG stated that it would be

very unlikely that both lobes would be treated in the same treatment session in UK practice owing to an increased risk of REILD. SIRT patients in the SARAH study[19] had 1.28 separate SIRT treatments on average [222 treatments, 173 patients (one or two treatments only)]. This broadly reflects the results of the Sirtex resource use survey (1.2 treatments per patient). This value excludes the 11 patients who had three separate SIRT treatments, and includes only one procedure for the nine patients who received a second treatment owing to disease progression, as it was unclear whether or not this would be permitted in UK practice.

The acquisition cost of a single SIRT treatment was taken from each company submission: SIR-Spheres, £8000; TheraSphere, £8000; and QuiremSpheres, £9896.

The cost of the SIRT procedure applied in the AG model was taken from *National Schedule of Reference Costs 2017–2018*[107] (YR57Z). The average cost of 'Percutaneous, Chemoembolisation, or Radioembolisation, of Lesion of Liver' was £2790. This cost was incurred for each separate SIRT administration for patients receiving TheraSphere and QuiremSpheres in the AG model. The Sirtex company submission[102] stated that SIR-Spheres administration procedures use intermittent contrast-medium injection to assess the distribution of the microspheres under radiography over the course of approximately 1 hour. The AG, therefore, included an additional cost of £209 for the SIR-Spheres administration procedure (RD32Z – Contrast Fluoroscopy Procedures with duration of more than 40 minutes), for a total of £2999.

Costs of systemic therapies

The pack costs for sorafenib (£3576.56), lenvatinib (£1437.00) and regorafenib (£3744.00) were taken from the BNF.[115] The confidential PAS discounts available for sorafenib, lenvatinib and regorafenib are not included in this report. For results of the AG's economic analysis that include these discounts, please refer to *Appendix 17*.

The daily dose of sorafenib used in the AG base case was based on the SARAH trial[19] (648.5 mg), and the mean time on treatment was calculated by applying an exponential function to the median time on treatment reported in the SARAH trial[19] (exponential mean 122.95 days).

The base-case daily dose of lenvatinib was 10.2 mg per day, based on the Western subgroup of the REFLECT trial[81] for lenvatinib. This value was considered by the technology appraisal committee in TA551[12] to better represent the average weight-based dose used in UK practice. The AG considered the time on treatment reported in the REFLECT trial[81] for lenvatinib to be excessively long compared with SARAH,[19] and reflective of differences in the baseline characteristics of the populations recruited to these trials. To avoid inflating the relative cost of lenvatinib, the AG applied the reported HR of PFS between lenvatinib and sorafenib in REFLECT to the SARAH time on treatment to produce an estimate of 124.07 days on treatment.

Wastage was accounted for in the AG model using the simple assumption that if a new pack was started then in the case of treatment discontinuation, the remainder could not be used to treat other patients. However, this may be a conservative assumption, as it was reported in TA555[13] that many centres have measures in place to reduce wastage of expensive cancer treatments, such as issuing only a 1-month supply of tablets at a time (approximately one pack of sorafenib). However, as it generally cannot be predetermined when therapy will be discontinued owing to AEs, death or non-compliance, it can be reasonably assumed that some wastage will occur.

Cost of subsequent treatment

The interventions used following first-line treatment in the SARAH trial[19] were not representative of current UK practice; however, as the efficacy data used in the model are derived from these patients, the trial values are most appropriate. Therefore, the proportion of patients who received subsequent systemic therapy (98% sorafenib) following SIRT in the SARAH trial[19] (28.8%) was used to estimate the size of this population in the AG model. The AG was advised that current NICE recommendations

mean that lenvatinib is rarely used in practice, as this would preclude second-line use of regorafenib. Therefore, 95% of patients continuing to subsequent systemic therapies following SIRT treatment are assumed to receive sorafenib, and 5% are assumed to receive lenvatinib.

As a number of chemotherapeutic/systemic agents administered to patients following sorafenib in the SARAH trial[19] have now been displaced in practice by regorafenib, or are otherwise no longer in use, the AG model assumes that the proportion of those who received systemic therapies after sorafenib in the trial (12.04%) would receive regorafenib in UK practice. A small proportion (3.47%; i.e. 12.04% of 28.8%) of SIRT patients also receive regorafenib following second-line sorafenib treatment. Duration of therapy and dose intensity of each of the three systemic agents modelled is assumed to be the same as first-line treatment, whereas regorafenib is assumed to have the same time on treatment as sorafenib (122.95 days), with a mean daily dose of 160 mg (RESORCE trial).[101]

Disease management costs

There are a number of issues with the health state unit costs used in previous technology appraisals in this indication, which precluded their use in the AG base case. The primary concern with these costs is that the original resource use surveys given to clinicians were based on the ongoing costs associated with sorafenib treatment. The resource use implications for systemic therapies may be very different with regard to monitoring and diagnostic testing to those for SIRT as a one-off procedure; therefore, these values may overestimate the disease management costs associated with the PFS health state for SIRT patients. Furthermore, the committee-preferred resource use data used in TA551[124] were collated from two resource use surveys conducted 10 years apart, generating very different estimates that may reflect differences in practice, costs and experience. As targeted therapies such as sorafenib were not yet in use at the time of this first survey, it is unlikely that these values are sufficiently representative of current practice.

In the light of these limitations, the AG used the results of a resource use survey conducted by Sirtex, which elicited information from 11 clinicians on the frequency and type of medical staff contact, monitoring and follow-up, hospitalisation frequency and length, and any use of PSS. Resource use pre progression, post progression and on progression were reported separately. Unit costs for each resource use item were derived from *National Schedule of Reference Costs 2017–2018*[107] and Personal Social Services Research Unit (PSSRU).[106] Differential costs were applied for systemic therapy patients during pre-progression, reflecting higher levels of ongoing diagnostic testing and additional follow-up contact.

The per-cycle post-progression costs applied in the AG model are significantly lower than those used in TA551[124] (£229.69 vs. £1268.16). This was driven primarily by greatly reduced use of hospital- and social care-based palliative care on progression since the original resource use survey. The health state costs used in the AG model are presented in *Table 29*.

TABLE 29 Assessment Group model health state costs

	Cost (£)			
Cost item	Pre-progression post SIRT (per cycle)	Pre-progression on systemic therapy (per cycle)	On progression (one off)	Progressive disease (per cycle)
Medical staff contact	47.30	58.18	54.51	102.55
Diagnostic procedures	59.92	61.90	41.07	2.83
Inpatient care	3.13	9.33	0.00	36.11
PSS	2.68	2.68	0.00	88.20
Total	113.03	132.10	95.57	229.69

A scenario that instead uses the committee-preferred costs from the lenvatinib appraisal is presented in *Sensitivity analyses results*.

Adverse event costs

Costs associated with the management of AEs were derived from previous NICE TAs of HCC,[11–13] using the latest *National Schedule of Reference Costs 2017–2018*[107] values or costs inflated to the 2018 cost year, where applicable. The AG base case used AE incidence rates from the SIR-Spheres arm of the SARAH trial[19] for the three SIRTs, and from the sorafenib arm of this trial for sorafenib. AE rates for lenvatinib were taken from the REFLECT trial.[81] For patients who received work-up but did not progress onto SIRT, the proportion of patients who received sorafenib incurred sorafenib AE management costs.

A full list of AE costs used in the AG model is presented in *Appendix 16*, *Table 75*.

Summary of Assessment Group base-case analysis inputs and assumptions

A summary of the resource use assumptions and costs applied in the AG base-case analysis is presented in *Table 30*.

TABLE 30 Summary of resource use and cost inputs in the AG model

Parameter	Treatment	Model input	Reference
Proportion of work-ups leading to SIRT	SIR-Spheres	81.4%	SARAH[19]
	TheraSphere	81.4%	SARAH[19]
	QuiremSpheres	81.4%	SARAH[19]
Treatment of SIRT work-up failure patients	Sorafenib	61.9%	SARAH[19]
	BSC	38.1%	AG assumption
Mean number of work-ups (treated patients)	SIR-Spheres	1.09	SARAH[19]
	TheraSphere	1.09	SARAH[19]
	QuiremSpheres	1.09	SARAH[19]
Mean number of SIRT procedures	SIR-Spheres	1.28	SARAH[19]
	TheraSphere	1.28	SARAH[19]
	QuiremSpheres	1.28	SARAH[19]
Subsequent systemic therapies			
Post SIRT	Sorafenib	27.4%	SARAH[19]/AG assumption
	Lenvatinib	1.4%	AG assumption
	Regorafenib (third line)	3.3%	AG assumption
	BSC	71.2%	AG assumption
Post sorafenib	Regorafenib	12.0%	AG assumption
	BSC	88.0%	AG assumption
Post lenvatinib	BSC	100%	AG assumption
Subsequent curative therapies			
Liver transplant		£16,556.07	*National Schedule of Reference Costs 2017–2018*[107]
Resection		£9676.59	*National Schedule of Reference Costs 2017–2018*[107]
Ablation		£2344.55	*National Schedule of Reference Costs 2017–2018*[107] (YG01A/YG01B)

continued

TABLE 30 Summary of resource use and cost inputs in the AG model (*continued*)

Parameter	Treatment	Model input	Reference
Treatment cost inputs			
Work-up	SIR-Spheres	£860.32	BTG elicitation (The Christie NHS Foundation Trust, personal communication)
	TheraSphere	£860.32	BTG elicitation (The Christie NHS Foundation Trust, personal communication)
	QuiremSpheres	£5178.32	BTG elicitation (The Christie NHS Foundation Trust, personal communication); Terumo submission[104]
Procedure	SIR-Spheres	£2999.00	*National Schedule of Reference Costs 2017–2018*[107] (YR57Z and RD32Z)
	TheraSphere	£2790.00	*National Schedule of Reference Costs 2017–2018*[107] (YR57Z)
	QuiremSpheres	£2790.00	*National Schedule of Reference Costs 2017–2018*[107] (YR57Z)
Acquisition (list price)	SIR-Spheres	£8000.00	Sirtex submission[102]
	TheraSphere	£8000.00	BTG submission[103]
	QuiremSpheres	£9896.00	Terumo submission[104]
	Sorafenib	£3576.56	BNF[115]
	Lenvatinib	£1437.00	BNF[115]
	Regorafenib	£3744.00	BNF[115]
Management costs			
AE costs (total)	SIR-Spheres	£477.69	NICE TA474,[11] TA514,[13] TA535,[154] TA551;[124] *National Schedule of Reference Costs 2017–2018*[107]
	TheraSphere	£477.69	NICE TA474,[11] TA514,[13] TA535,[154] TA551;[124] *National Schedule of Reference Costs 2017–2018*[107]
	QuiremSpheres	£477.69	NICE TA474,[11] TA514,[13] TA535,[154] TA551;[124] *National Schedule of Reference Costs 2017–2018*[107]
	Sorafenib	£932.79	NICE TA474,[11] TA514,[13] TA535,[154] TA551;[124] *National Schedule of Reference Costs 2017–2018*[107]
	Lenvatinib	£542.08	NICE TA474,[11] TA514,[13] TA535,[154] TA551;[124] *National Schedule of Reference Costs 2017–2018*[107]
	Sorafenib/BSC (work-up/no SIRT)	£577.40	NICE TA474,[11] TA514,[13] TA535,[154] TA551;[124] *National Schedule of Reference Costs 2017–2018*[107]
Health state costs (per cycle)	PFS (SIRT)	£113.03	Sirtex expert elicitation; *National Schedule of Reference Costs 2017–2018*,[107] PSSRU 2018[106]
	PFS (systemic therapies)	£132.10	Sirtex expert elicitation; *National Schedule of Reference Costs 2017–2018*,[107] PSSRU 2019[106]
	On progression	£95.57	Sirtex expert elicitation; *National Schedule of Reference Costs 2017–2018*,[107] PSSRU 2020[106]
	Post progression	£229.69	Sirtex expert elicitation; *National Schedule of Reference Costs 2017–2018*,[107] PSSRU 2021[106]
	End of life	£8191.00	Georghiou and Bardsley[128]
	Postcurative therapy (scenario)	£113.03	Sirtex expert elicitation; *National Schedule of Reference Costs 2017–2018*[107]

Analytic methods

Base-case analysis

The AG produced fully incremental ICERs for each strategy included in the model; however, this approach generated a number of ICERs expressed in terms of dominance owing to the close similarity of health outcomes predicted for the SIRTs.

The AG, therefore, considered a net benefit framework to be the most appropriate approach to present the relative cost-effectiveness of the three SIRTs with existing practice. This method is often preferred when there are a number of technologies under comparison, particularly when incremental costs and benefits are very similar. Technologies with identical health outcomes and marginal differences in costs are often labelled as 'dominant/dominated' using incremental cost-effectiveness analysis with conventional decision rules. Considering net health benefit instead permits a more informative comparison of the effect of alternative strategies.

Net monetary benefit is calculated using a rearrangement of the ICER formula, but inherently compares the incremental health gain with the comparator with a willingness-to-pay (WTP) threshold. The NMB formula thereby assigns a value to the additional QALYs generated by an intervention, and considers the opportunity cost associated with generating these health benefits. The formula used to define NMB is $\lambda \times \Delta E - \Delta C$, where the difference in health effects (ΔE) is multiplied by the selected WTP threshold (λ) minus the difference in costs (ΔC) (i.e. £30,000 in the results presented below). Using this approach, if an intervention has an incremental NMB of > 0, then it would be considered more cost-effective than the baseline option, in this case the least costly option. NMB results (including PAS discounts) at a £20,000 and £30,000 threshold are also presented in *Appendix 17*.

The AG model accounted for uncertainty using probabilistic and deterministic sensitivity analyses. PSA was undertaken using simple Monte Carlo sampling methods, using 20,000 samples for the AG base case and 5000 samples in the primary scenario analyses. The choice of distribution to reflect uncertainty around each parameter was selected for each according to its statistical suitability. To account for uncertainty around the parametric survival models fitted to OS and PFS, outcomes were sampled via Cholesky decomposition using the variance–covariance matrices produced during survival modelling. When a HR was used to estimate PFS and OS outcomes, alternate values were drawn in each model iteration from the NMA output from WinBUGS (CODA) to model uncertainty in the predicted treatment effects.

Model validation

The AG adopted a number of approaches to ensure the credibility and validity of the model. These included scrutiny of the implemented model coding and formulae by two modellers, black-box testing in which the predictive validity of parameter inputs (e.g. that increasing effectiveness of the treatment lowers cost-effectiveness) was assessed, checking the accuracy of all model inputs against the original sources and consultation with clinical experts on key assumptions (see *Acknowledgements*).

Results of the independent economic assessment

Base-case results

The deterministic and probabilistic fully incremental results of the AG's base-case analysis (excluding confidential PAS discounts for QuiremScout, sorafenib, lenvatinib and regorafenib) are presented in *Table 31*. The probabilistic results were based on 20,000 model iterations.

TABLE 31 Fully incremental results of the AG's base-case analysis

Intervention	Total			Incremental (vs. baseline)				ICER (£) (fully incremental)
	Costs (£)	Life-years	QALYs	Costs (£)	QALYs	ICER (£)	NMB (£)	
AG deterministic base case								
TheraSphere	29,888	1.110	0.764					
Lenvatinib	30,005	1.183	0.805	117	0.04	2911	1090	2911
SIR-Spheres	30,107	1.110	0.764	218	0.000	More costly	−218	Extendedly dominated
Sorafenib	32,082	1.243	0.841	2194	0.076	28,728	97	57,488
QuiremSpheres	36,503	1.110	0.764	6614	0.000	More costly	−6614	Extendedly dominated
AG probabilistic base case								
Lenvatinib	29,658	1.202	0.825					
TheraSphere	30,014	1.111	0.765	356	−0.060	Dominated	−2154	Dominated
SIR-Spheres	30,196	1.111	0.765	538	−0.060	Dominated	−2323	Dominated
Sorafenib	32,444	1.244	0.841	2786	0.016	174,320	−2306	174,320
QuiremSpheres	36,613	1.111	0.765	6955	−0.060	Dominated	−8741	Dominated

The AG's base case was based on the following assumptions and data sources:

- SIR-Spheres efficacy based on a pooled survival analysis of SARAH[19] and SIRveNIB[21] data (per-protocol population)
- QuiremSpheres and TheraSphere efficacy equal to SIR-Spheres
- for patients who received work-up but no SIRT, OS and PFS based on SARAH[19] KM
- sorafenib efficacy based on a pooled survival analysis of SARAH[19] and SIRveNIB[21] data (ITT population)
- lenvatinib HR derived from the AG's NMA (ITT population)
- OS and PFS extrapolated using a Weibull model
- decision tree transition probabilities estimated using data from the SARAH[19] trial
- no downstaging to curative therapy permitted
- bilobar treatments performed in two separate procedures
- work-up costs from The Christie NHS Foundation Trust elicitation (as per the BTG economic analysis)
- health state utilities from the SARAH[19] per-protocol subgroup, based on therapeutic class (SIRT and systemic therapy).

Based on the probabilistic version of the AG model, the three SIRTs are each expected to generate fewer QALYs than sorafenib or lenvatinib, but were associated with higher costs. SIRT generated 0.765 QALYs; this was 0.076 QALYs fewer than generated by sorafenib and 0.060 fewer than by lenvatinib. TheraSphere and SIR-Spheres had very similar total costs, and QuiremSpheres was the most costly owing to the additional costs associated with procurement of QuiremScout.

Figure 19 presents CEACs for the fully incremental results of the AG model. Lenvatinib has the highest likelihood of being cost-effective across any WTP threshold of < £100,000. Assuming a WTP threshold of £30,000 per QALY gained, TheraSphere had an incremental NMB of −£2154, and this was −£2323 for SIR-Spheres. The NMB for QuiremSpheres versus lenvatinib was −£8741. All three SIRTs were dominated by lenvatinib. Disaggregated deterministic results show that just under half of the QALY gain in both groups is accrued in the post-progression health state.

For results including the confidential PAS discounts for sorafenib, lenvatinib, regorafenib and QuiremSpheres, see *Appendix 17*.

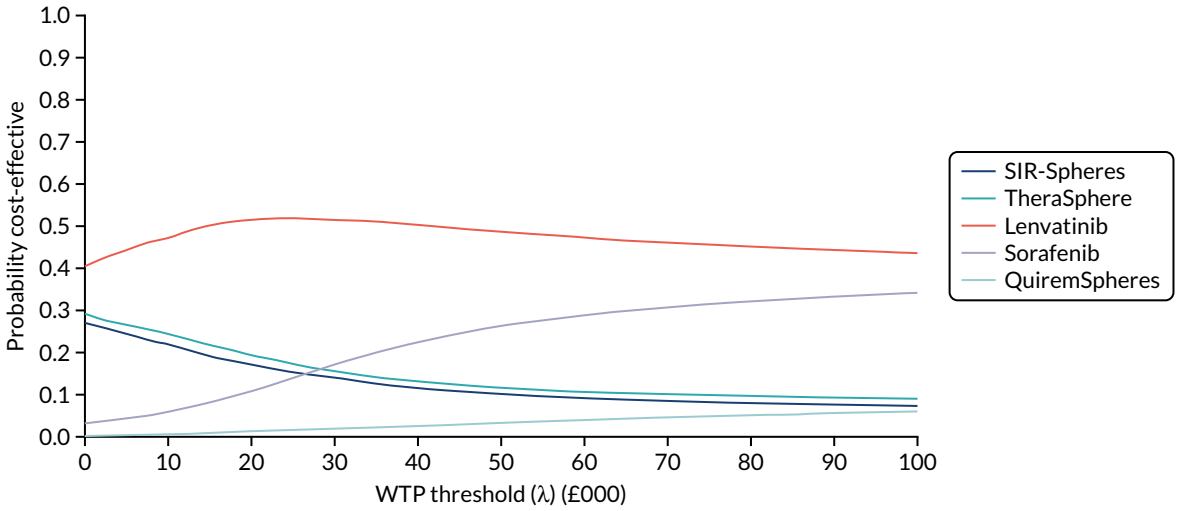

FIGURE 19 Cost-effectiveness acceptability curve for the AG probabilistic base-case analysis.

Sensitivity analyses results

Scenario analyses

Scenario 1: efficacy data from SARAH only

The first scenario analysis explores the effect of using only data from the European SARAH trial[19] to inform efficacy estimates for SIRT and sorafenib, on the basis that these might better represent the patient population and clinical practice in the UK. Deterministic and probabilistic results are presented in *Table 32*. The probabilistic results are based on 5000 model iterations. As with the AG base case, each SIRT is associated with almost the same number of life-years and QALYs; however, this scenario predicts lower OS (and thus life-years/QALYs) than in the base case, which makes SIR-Spheres marginally cheaper than lenvatinib.

TABLE 32 Assessment Group scenario 1 results: efficacy data from SARAH only

	Total			Incremental (vs. baseline)				
Intervention	Costs (£)	Life-years	QALYs	Costs (£)	QALYs	ICER (£)	NMB (£)	ICER (£) (fully incremental)
Deterministic scenario 1: efficacy data from SARAH only								
TheraSphere	29,395	0.976	0.671					
SIR-Spheres	29,614	0.976	0.671	218	0.000	More costly	−218	Extendedly dominated
Lenvatinib	29,893	1.150	0.782	498	0.111	4475	2840	4475
Sorafenib	31,951	1.209	0.817	2556	0.147	17,424	1845	58,080
QuiremSpheres	36,010	0.976	0.671	6614	0.000	More costly	−6614	Extendedly dominated
Probabilistic scenario 1: efficacy data from SARAH only								
Lenvatinib	29,413	1.171	0.805					
TheraSphere	29,476	0.978	0.672	62	−0.133	Dominated	−4044	Dominated
SIR-Spheres	29,660	0.977	0.671	246	−0.134	Dominated	−4267	Dominated
Sorafenib	32,300	1.213	0.818	2887	0.014	212,505	−2479	212,505
QuiremSpheres	36,064	0.977	0.670	6650	−0.134	Dominated	−10,684	Dominated

Scenario 2: low tumour burden/albumin–bilirubin 1 subgroup (SARAH)

This scenario explores the use of the company's preferred post hoc grouping of patients from the SARAH trial[19] as the source of efficacy data for SIRT and sorafenib. Further changes from the AG base case are the use of the higher low tumour burden/ALBI 1 subgroup utilities from the SARAH trial,[19] and the significantly lower proportion of patients who receive work-up but not SIRT (8.1% vs. 18.6%). Note that although Sirtex used a proportion of 2.9% for work-up failures in this population, it was unclear how this figure was reached. Increasing the number of work-up failures, however, increases the cost-effectiveness of SIRT.

This scenario predicts the cost-effectiveness of an optimised decision in which only patients who have a tumour burden of $\leq$ 25% and a preserved liver function would be eligible to receive SIRT. As there is no equivalent evidence available for lenvatinib, this scenario assumes that the HR between sorafenib and lenvatinib remains the same as in the base-case population.

Table 33 shows that although the systemic therapies were less costly than SIRT in this scenario, SIR-Spheres generated an additional 0.139 QALYs compared with lenvatinib and 0.117 compared with sorafenib in the probabilistic model. This resulted in fully incremental ICERs of £20,926 per QALY gained for TheraSphere compared with lenvatinib, and £119,562 for SIR-Spheres compared with TheraSphere. However, the two technologies were distinguished only by the additional fluoroscopy cost associated with the SIR-Spheres procedure, resulting in very similar NMB at a £30,000 threshold. This is notably the only scenario in which TheraSphere and SIR-Spheres have a positive incremental NMB versus lenvatinib at a WTP threshold of £30,000 (excluding scenario 4). This is illustrated by the CEAC in *Figure 20*, which shows lenvatinib to have the highest likelihood of being cost-effective up to a WTP threshold of approximately £27,000, at which point it is surpassed by TheraSphere and by SIR-Spheres at a WTP threshold of $\geq$ £32,000.

Results including the confidential PAS discounts for sorafenib, lenvatinib, regorafenib and QuiremSpheres can be found in *Appendix 17*.

TABLE 33 Assessment Group scenario 2 results: low tumour burden/ALBI 1 subgroup

	Total		Incremental (vs. baseline)					
Intervention	Costs (£)	Life-years	QALYs	Costs (£)	QALYs	ICER (£)	NMB (£)	ICER (£) (fully incremental)
Deterministic scenario 2: low tumour burden/ALBI 1 subgroup								
Lenvatinib	31,388	1.366	1.000					
Sorafenib	33,388	1.420	1.037	2000	0.038	53,320	–875	Extendedly dominated
TheraSphere	34,021	1.542	1.153	2633	0.153	17,175	1966	17,175
SIR-Spheres	34,267	1.542	1.153	2879	0.153	18,783	1720	Dominated
QuiremSpheres	40,931	1.542	1.153	9543	0.153	62,257	–4945	Dominated
Probabilistic scenario 2: low tumour burden/ALBI 1 subgroup								
Lenvatinib	31,233	1.397	1.024					
Sorafenib	33,834	1.436	1.048	2601	0.024	109,709	–1890	Extendedly dominated
TheraSphere	34,086	1.552	1.161	2854	0.136	20,926	1237	20,926
SIR-Spheres	34,389	1.553	1.163	3156	0.139	22,725	1010	119,562
QuiremSpheres	41,088	1.552	1.162	9855	0.138	71,372	–5712	Extendedly dominated

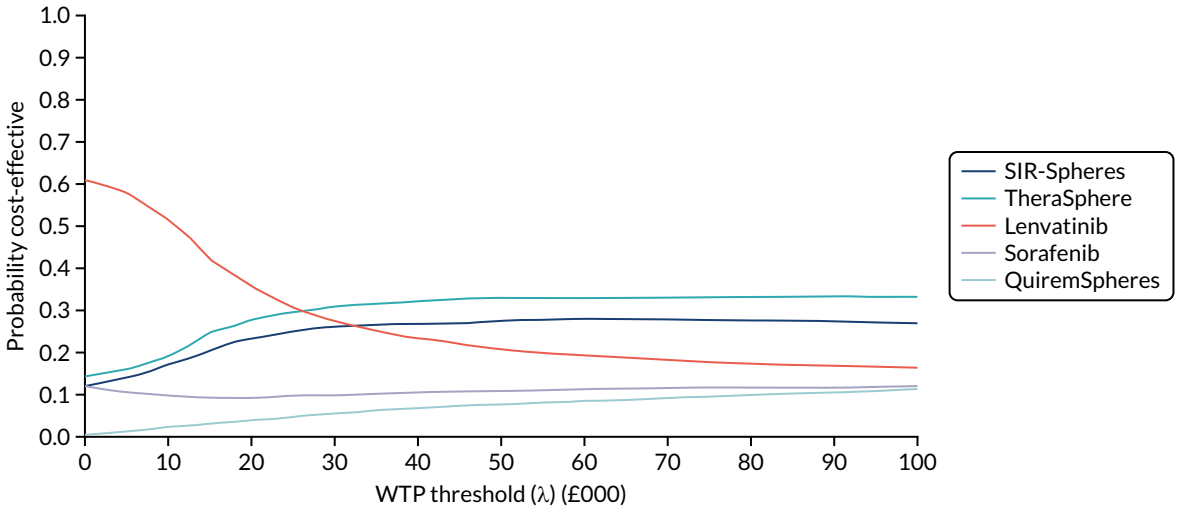

FIGURE 20 Cost-effectiveness acceptability curve for AG scenario 2: low tumour burden/ALBI 1 subgroup.

Scenario 3: no macroscopic vascular invasion (SARAH)

This scenario limits the patient population to only those who had no MVI, referred to elsewhere as PVI, at baseline. These patients may be expected to benefit more from SIRT owing to a more favourable positioning and spread of their tumour, and were thus defined as a subgroup of interest in NICE's scope. As there is no equivalent evidence for lenvatinib, this scenario assumes that the HR between sorafenib and lenvatinib remains the same as in the base-case population.

The probabilistic analysis in *Table 34* found all three SIRTs to be dominated by lenvatinib, with a significantly lower NMB than either systemic therapy. Notably, the gap in QALYs produced by SIRT versus sorafenib widened in this analysis versus the base case, implying a reduced benefit of SIRT in this population.

TABLE 34 Assessment Group scenario 3 results: no MVI

	Total			Incremental (vs. baseline)				
Intervention	Costs (£)	Life-years	QALYs	Costs (£)	QALYs	ICER (£)	NMB (£)	ICER (£) (fully incremental)
Deterministic scenario 3: no MVI (SARAH)								
TheraSphere	29,949	1.078	0.740					
SIR-Spheres	30,167	1.078	0.740	218	0.000	More costly	−218	Extendedly dominated
Lenvatinib	30,399	1.272	0.865	451	0.125	3594	3310	3594
Sorafenib	32,452	1.326	0.897	2503	0.157	15,923	2213	64,437
QuiremSpheres	36,563	1.078	0.740	6614	0.000	More costly	−6614	Extendedly dominated
Probabilistic scenario 3: no MVI (SARAH)								
Lenvatinib	29,985	1.295	0.888					
TheraSphere	30,094	1.086	0.746	109	−0.142	Dominated	−4382	Dominated
SIR-Spheres	30,314	1.086	0.746	329	−0.143	Dominated	−4616	Dominated
Sorafenib	32,876	1.335	0.905	2890	0.017	170,117	−2381	170,117
QuiremSpheres	36,662	1.086	0.745	6676	−0.143	Dominated	−10,965	Dominated

Scenario 4: TheraSphere hazard ratio from the Biederman et al. *and Van Der Gucht* et al. *network meta-analysis scenario*

The results presented in *Table 35* use the HR derived from the AG's NMA scenario, which included the low-quality retrospective studies by Biederman *et al.*[39] and Van Der Gucht *et al.*[40] The patient population in Biederman *et al.*[39] was particularly mismatched with the others included in this analysis, as it included only patients with MVI, which appeared to have a substantial impact on the treatment effect associated with TheraSphere.

A HR of 0.46 versus SIR-Spheres was applied for both OS and PFS outcomes for TheraSphere. Based on the probabilistic analysis (5000 iterations), TheraSphere is expected to generate an additional 0.507 QALYs compared with lenvatinib, at an additional cost of £4068, producing an ICER of £8017 per QALY gained, and a NMB of £11,413. TheraSphere was associated with higher costs than SIR-Spheres owing to the increased disease management costs associated with lower mortality, but it also produced an additional 0.566 QALYs, yielding an ICER of £6060 per QALY gained.

Further scenario analyses

Table 36 presents a number of other scenarios on the AG base case that explore the impact of alternative assumptions, including sources of utilities, downstaging to curative therapy, resource use and survival models.

Scenarios 6 and 10 include the possibility for downstaging; in these scenarios, the distribution of the three liver-targeted treatments was derived from the SARAH trial.[19] Patients who received TACE or radiation therapy were excluded as these would not be permitted options in this population in UK practice. Liver transplant was undergone by 1.09% of SIRT patients and 0.46% of sorafenib patients; 1.63% of SIRT patients and 0% of sorafenib patients underwent liver resection, and 3.26% of SIRT patients and 0.92% of sorafenib patients received ablation therapy.

Only the deterministic results are produced for these analyses.

TABLE 35 Assessment Group scenario 4 results: TheraSphere HR from Biederman *et al.*[39] and Van Der Gucht *et al.*[40] NMA scenario

	Total			Incremental (vs. baseline)				
Intervention	Costs (£)	Life-years	QALYs	Costs (£)	QALYs	ICER (£)	NMB (£)	ICER (£) (fully incremental)
Deterministic scenario 4: TheraSphere HR from Biederman* et al. *and Van Der Gucht* et al. *NMA scenario								
Lenvatinib	30,005	1.183	0.805					
SIR-Spheres	30,107	1.110	0.764	101	−0.040	Dominated	−1308	Dominated
Sorafenib	32,082	1.243	0.841	2077	0.036	57,488	−993	Extendedly dominated
TheraSphere	33,373	1.883	1.297	3368	0.493	6835	11,413	6835
QuiremSpheres	36,503	1.110	0.764	6497	−0.040	Dominated	−7705	Dominated
Probabilistic scenario 4: TheraSphere HR from Biederman* et al. *and Van Der Gucht* et al. *NMA scenario								
Lenvatinib	29,601	1.197	0.822					
SIR-Spheres	30,242	1.110	0.764	641	−0.058	Dominated	−2387	Dominated
Sorafenib	32,477	1.244	0.843	2876	0.021	140,205	−2260	Extendedly dominated
TheraSphere	33,670	1.931	1.330	4068	0.507	8017	11,156	8017
QuiremSpheres	36,616	1.111	0.765	7014	−0.058	Dominated	−8746	Dominated

TABLE 36 Further scenario analyses (AG scenarios 5–17)

Intervention	Total			Incremental (vs. baseline)				ICER (£) (fully incremental)
	Costs (£)	Life-years	QALYs	Costs (£)	QALYs	ICER (£)	NMB (£)	
Scenario 5: utilities from lenvatinib TA551[124]								
TheraSphere	29,888	1.110	0.791					
Lenvatinib	30,005	1.183	0.846	117	0.055	2113	1546	2113
SIR-Spheres	30,107	1.110	0.791	218	0.000	More costly	−218	Extendedly dominated
Sorafenib	32,082	1.243	0.881	2194	0.091	24,145	532	58,615
QuiremSpheres	36,503	1.110	0.791	6614	0.000	More costly	−6614	Extendedly dominated
Scenario 6: downstaging to curative therapy possible (SARAH[19] ITT proportions)								
TheraSphere	28,990	1.217	0.842					
SIR-Spheres	29,208	1.217	0.842	218	0.000	More costly	−218	Extendedly dominated
Lenvatinib	29,817	1.212	0.826	827	−0.016	Dominated	−1292	Dominated
Sorafenib	31,850	1.271	0.862	2860	0.020	142,238	−2256	142,238
QuiremSpheres	35,605	1.217	0.842	6614	0.000	More costly	−6614	Extendedly dominated
Scenario 7: bilobar disease treated in same procedure								
TheraSphere	29,159	1.110	0.764					
SIR-Spheres	29,364	1.110	0.764	204	0.000	More costly	−204	Extendedly dominated
Lenvatinib	30,005	1.183	0.805	846	0.040	21,026	361	21,026
Sorafenib	32,082	1.243	0.841	2923	0.076	38,274	−632	57,488
QuiremSpheres	35,646	1.110	0.764	6486	0.000	More costly	−6486	Extendedly dominated
Scenario 8: work-up costs from* National Schedule of Reference Costs 2017–2018[107] *(Sirtex assumption)								
Lenvatinib	30,005	1.183	0.805					
TheraSphere	30,170	1.110	0.764	165	−0.040	Dominated	−1372	Dominated
SIR-Spheres	30,389	1.110	0.764	383	−0.040	Dominated	−1590	Dominated
Sorafenib	32,082	1.243	0.841	2077	0.036	57,488	−993	57,488
QuiremSpheres	36,864	1.110	0.764	6859	−0.040	Dominated	−8066	Dominated
Scenario 9: disease management costs taken from TA551[124]								
Lenvatinib	48,033	1.183	0.805					
TheraSphere	48,186	1.110	0.764	152	−0.040	Dominated	−1360	Dominated
SIR-Spheres	48,404	1.110	0.764	371	−0.040	Dominated	−1578	Dominated
Sorafenib	53,682	1.243	0.841	5649	0.036	156,367	−4565	156,367
QuiremSpheres	54,800	1.110	0.764	6767	−0.040	Dominated	−7974	Dominated

continued

TABLE 36 Further scenario analyses (AG scenarios 5–17) (*continued*)

Intervention	Total			Incremental (vs. baseline)				ICER (£) (fully incremental)
	Costs (£)	Life-years	QALYs	Costs (£)	QALYs	ICER (£)	NMB (£)	
Scenario 10: low tumour burden/ALBI 1 subgroup including possibility of downstaging								
Lenvatinib	31,072	1.404	1.029					
TheraSphere	31,467	1.736	1.303	395	0.274	1440	7826	1440
SIR-Spheres	31,713	1.736	1.303	641	0.274	2339	7579	Dominated
Sorafenib	33,007	1.457	1.066	1935	0.037	52,685	−833	Extendedly dominated
QuiremSpheres	38,377	1.736	1.303	7305	0.274	26,660	915	Dominated
Scenario 11: Gompertz OS								
TheraSphere	30,015	1.127	0.776					
Lenvatinib	30,066	1.188	0.808	51	0.033	1555	926	1555
SIR-Spheres	30,234	1.127	0.776	218	0.000	More costly	−218	Extendedly dominated
Sorafenib	32,190	1.255	0.849	2174	0.073	29,634	27	52,020
QuiremSpheres	36,630	1.127	0.776	6614	0.000	More costly	−6614	Extendedly dominated
Scenario 12: exponential OS								
Lenvatinib	30,239	1.215	0.826					
TheraSphere	30,245	1.160	0.798	5	−0.028	Dominated	−860	Dominated
SIR-Spheres	30,463	1.160	0.798	224	−0.028	Dominated	−1078	Dominated
Sorafenib	32,379	1.285	0.868	2139	0.042	50,493	−868	50,493
QuiremSpheres	36,859	1.160	0.798	6620	−0.028	Dominated	−7474	Dominated
Scenario 13: generalised gamma OS (lenvatinib OS equal to sorafenib)								
TheraSphere	30,992	1.277	0.875					
Lenvatinib	31,148	1.357	0.919	155	0.044	3561	1154	3561
SIR-Spheres	31,211	1.277	0.875	218	0.000	More costly	−218	Extendedly dominated
Sorafenib	32,854	1.357	0.916	1862	0.040	46,103	−650	Extendedly dominated
QuiremSpheres	37,607	1.277	0.875	6614	0.000	More costly	−6614	Extendedly dominated
Scenario 14: log-normal OS (lenvatinib OS equal to sorafenib)								
TheraSphere	30,208	1.156	0.795					
SIR-Spheres	30,426	1.156	0.795	218	0.000	More costly	−218	Extendedly dominated
Lenvatinib	31,480	1.408	0.952	1273	0.158	8078	3454	8078
Sorafenib	33,187	1.408	0.949	2979	0.154	19,311	1649	Extendedly dominated
QuiremSpheres	36,822	1.156	0.795	6614	0.000	More costly	−6614	Extendedly dominated

TABLE 36 Further scenario analyses (AG scenarios 5–17) (*continued*)

Intervention	Total			Incremental (vs. baseline)				ICER (£) (fully incremental)
	Costs (£)	Life-years	QALYs	Costs (£)	QALYs	ICER (£)	NMB (£)	
Scenario 15: log-logistic OS (lenvatinib OS equal to sorafenib)								
TheraSphere	30,301	1.169	0.804					
SIR-Spheres	30,519	1.169	0.804	218	0.000	More costly	−218	Extendedly dominated
Lenvatinib	31,543	1.420	0.960	1242	0.156	7962	3439	7962
Sorafenib	33,249	1.420	0.956	2949	0.153	19,303	1634	Extendedly dominated
QuiremSpheres	36,915	1.169	0.804	6614	0.000	More costly	−6614	Extendedly dominated
Scenario 16: 5% work-up/no SIRT								
Lenvatinib	30,005	1.183	0.805					
Sorafenib	32,082	1.243	0.841	2077	0.036	57,488	−993	57,488
TheraSphere	32,603	1.183	0.816	2597	0.011	239,222	−2272	Extendedly dominated
SIR-Spheres	32,858	1.183	0.816	2852	0.011	262,683	−2526	Extendedly dominated
QuiremSpheres	39,601	1.183	0.816	9596	0.011	883,746	−9270	Extendedly dominated
Scenario 17: SIRveNIB[21] work-up/no SIRT (28.57%)								
TheraSphere	27,898	1.056	0.727					
SIR-Spheres	28,090	1.056	0.727	192	0.000	More costly	−192	Extendedly dominated
Lenvatinib	30,005	1.183	0.805	2107	0.078	27,118	224	27,118
Sorafenib	32,082	1.243	0.841	4184	0.114	36,757	−769	57,488
QuiremSpheres	34,232	1.056	0.727	6333	0.000	More costly	−6333	Dominated

Table 37 presents the results of the base-case and selected scenario analyses in terms of their effect on the NMB ranking of the five technologies at list price. This shows lenvatinib to be consistently ranked first in terms of incremental NMB, except in those scenarios that use more favourable assumptions in favour of SIRT. As SIRT produces QALYs above the WTP threshold, increasing the proportion of patients who fail work-up (scenario 17) and do not go on to receive SIRT increases its cost-effectiveness, as overall costs are reduced and the more cost-effective QALYs produced on BSC and sorafenib are up-weighted.

Deterministic sensitivity analysis

Results of the DSAs are presented in *Figures 21–25* for the AG base-case scenario and the four scenarios presented in *Scenario analyses*. The tornado diagrams present the 10 most influential parameters in each analysis. SIR-Spheres was compared with sorafenib because sorafenib was considered the most relevant comparator and had direct evidence compared with SIR-Spheres.

TABLE 37 Incremental NMB rankings

Intervention	Incremental NMB rank (vs. baseline)																	
	Base case	S1	S2	S3	S4	S5	S6	S7	S8	S9	S10	S11	S12	S13	S14	S15	S16	S17
SIR-Spheres	4	4	2	4	4	4	2	3	4	3	2	4	4	3	4	4	4	3
TheraSphere	2	3	1	3	1	3	1	2	3	2	1	3	3	2	3	3	3	2
QuiremSpheres	5	5	5	5	5	5	5	5	5	5	3	5	5	5	5	5	5	5
Lenvatinib	1	1	3	1	2	1	3	1	1	1	4	1	1	1	1	1	1	1
Sorafenib	3	2	4	2	3	2	4	4	2	4	5	2	2	4	2	2	2	4

S, scenario.

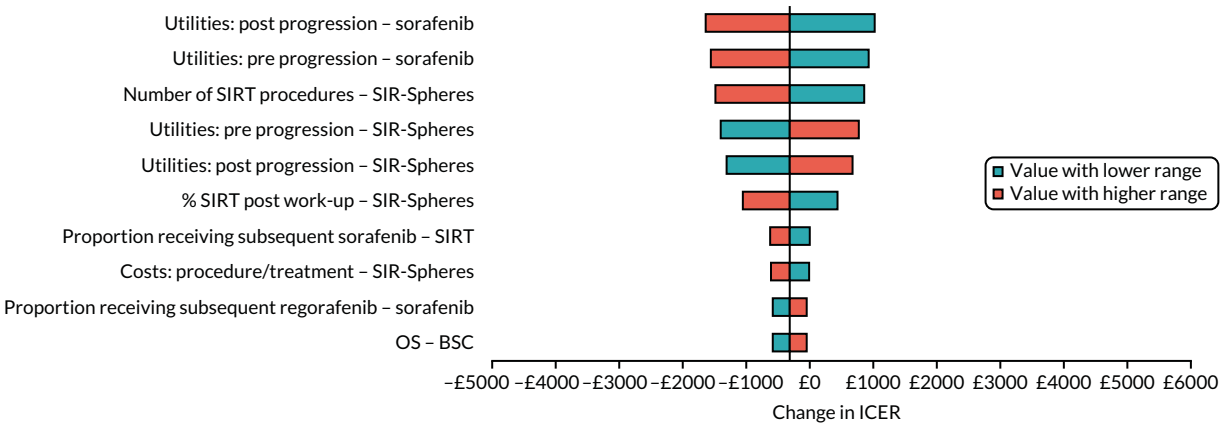

FIGURE 21 Tornado diagram: SIR-Spheres vs. sorafenib; base-case analysis (SARAH[19] and SIRveNIB[21]).

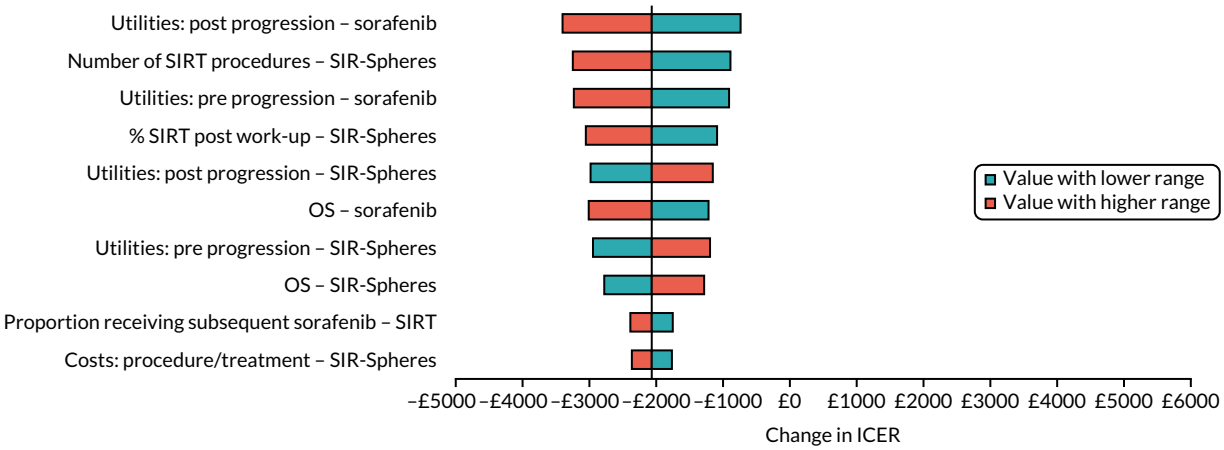

FIGURE 22 Tornado diagram: SIR-Spheres vs. sorafenib; using SARAH[19] efficacy data (scenario 1).

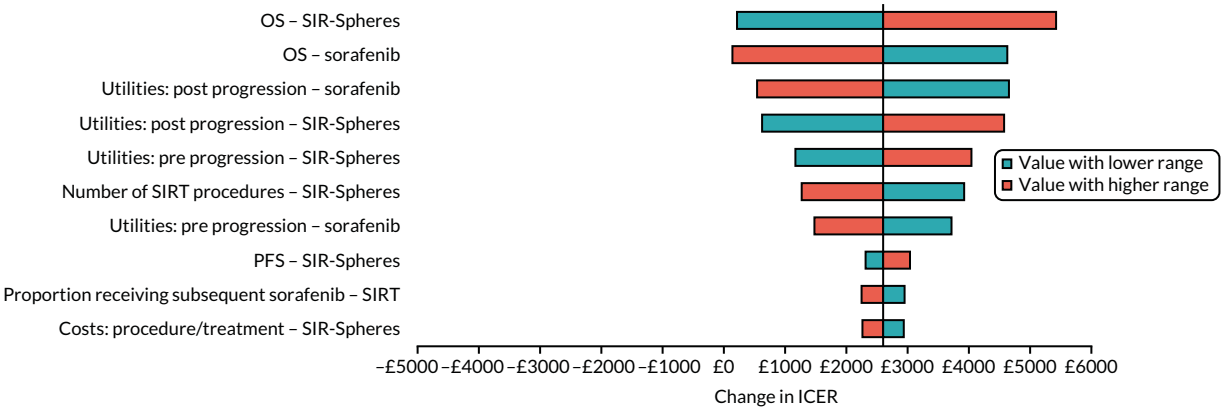

FIGURE 23 Tornado diagram: SIR-Spheres vs. sorafenib; low tumour burden/ALBI 1 subgroup (scenario 2).

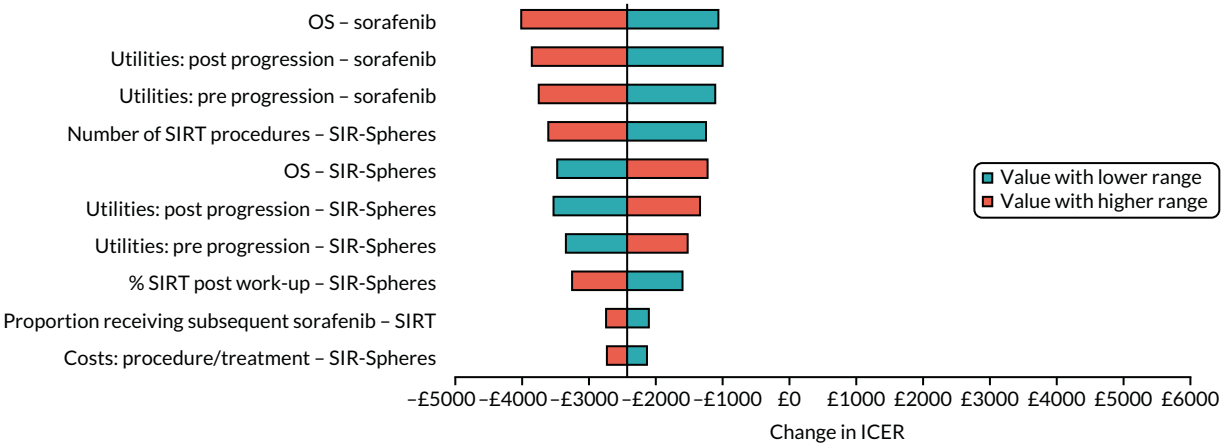

FIGURE 24 Tornado diagram: SIR-Spheres vs. sorafenib; no MVI subgroup (scenario 3).

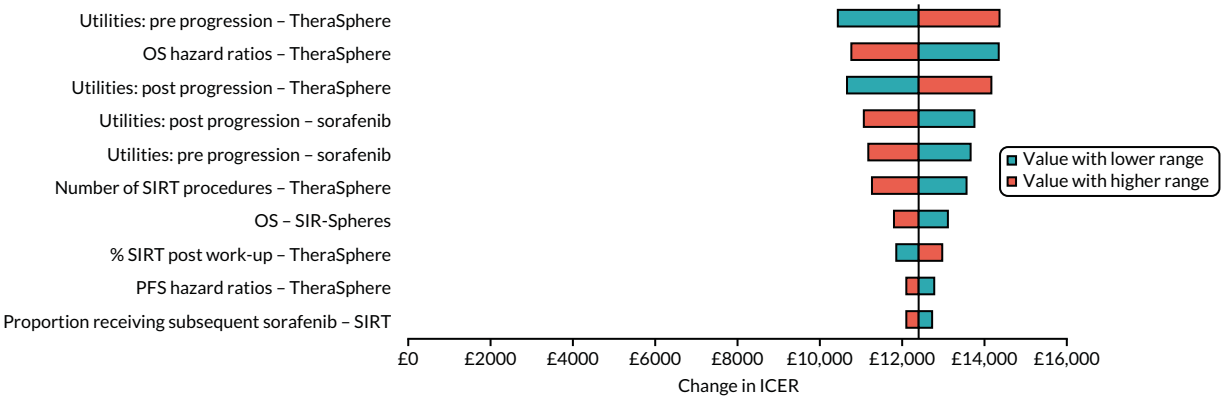

FIGURE 25 Tornado diagram: TheraSphere vs. sorafenib; TheraSphere HR from Van Der Gucht *et al.*[40] and Biederman *et al.*[39] NMA (scenario 4).

The AG base-case analysis (see *Figure 21*) was robust to a range of parameters, with the most influential parameters providing a range of NMBs between approximately –£1600 and £1000, with the base-case NMB as –£315. The most influential parameters were the health state utilities, the number of SIRT procedures and the proportion of patients receiving SIRT after work-up. In these scenarios, SIR-Spheres became cost-effective compared with sorafenib for some of the range of values of the parameter (i.e. SIR-Spheres had a positive incremental NMB). However, when the confidential PAS for sorafenib was applied, this was no longer the case.

In scenario 1, with efficacy data based only on SARAH[19], varying the parameters in the DSA had a larger impact on NMB than in the base-case analysis, although the variation remains small (see *Figure 22*). Similarly to the base-case analysis, the results were most sensitive to health state utilities and SIRT procedures; however, in this analysis, OS for sorafenib and SIR-Spheres was also an influential parameter. There were no scenarios in which SIR-Spheres was estimated to be cost-effective compared with sorafenib.

The most influential parameter in the low tumour burden/ALBI 1 subgroup was OS for both SIR-Spheres and sorafenib (see *Figure 23*). SIR-Spheres remained cost-effective compared with sorafenib over the range of parameters; however, when the confidential PAS for sorafenib was applied, this was no longer the case.

In the 'no-MVI' subgroup, the most influential parameters were the health state utilities and OS for sorafenib and SIR-Spheres (see *Figure 24*). There were are no scenarios in which SIR-Spheres was estimated to be cost-effective compared with sorafenib.

In *Figure 25*, TheraSphere was compared with sorafenib. In this scenario, the results of the analysis were robust to the range of parameters, and found TheraSphere to be cost-effective across all scenarios.

Discussion of the independent economic assessment

In the light of the AG's concerns regarding the relevance of the economic analyses identified in the review of cost-effectiveness studies and highlighted limitations in the economic evaluations developed by BTG and Sirtex, the AG developed a de novo health economic model. The AG model evaluated the three SIRTs and current UK practice for the treatment of advanced HCC in Child–Pugh class A patients ineligible to receive (or who had previously failed) CTT. Results were generated as fully incremental ICERs and in terms of incremental NMB, which allows for easier comparison of 'dominated' results with small differences in cost and efficacy. The AG model used a three-state partitioned survival model approach with a decision tree, which determined the proportion of patients who did not continue on to receive SIRT following the work-up procedure. The model utilises all currently available RCT evidence to generate estimates of clinical effectiveness, using data directly drawn from the SARAH[19] and SIRveNIB[21] trials, and HRs generated in the AG's NMA.

Based on the AG's probabilistic base-case analysis at list price, none of the three SIRTs is expected to be cost-effective at any WTP threshold, being more costly and less effective than lenvatinib. When the modelled population was limited to only those with a low tumour burden and preserved liver function, the ICERs for TheraSphere and SIR-Spheres were £17,165 and £18,783 per QALY gained versus the most cost-effective systemic therapy. The most optimistic ICERs were generated in the scenario presented for the low tumour burden and preserved liver function in which downstaging to curative therapy was permitted. In this scenario, the ICERs for TheraSphere and SIR-Spheres decreased to £1440 and £2339, respectively. However, there was no scenario in which SIRT was predicted to be cost-effective at a WTP threshold of £30,000 when confidential PAS discounts were included (see *Appendix 17*). In all scenarios, QuiremSpheres was not cost-effective compared with other SIRTs owing to higher work-up and acquisition costs (see below for further discussion of QuiremSpheres in relation to the limitations of the model).

The AG scenario 4 (including the Biederman *et al.*[39] and Van Der Gucht *et al.*[40] studies) found TheraSphere to be cost-effective versus lenvatinib when the confidential PAS prices were used. However, the AG considers the data used to model comparative effectiveness to be of low quality and inconsistent with the wider body of evidence on the comparative effectiveness of SIR-Spheres and TheraSphere. The AG, therefore, does not consider this scenario to represent a realistic estimate of the relative benefits of TheraSphere.

The results of the AG's base-case analysis are robust to a wide range of assumptions, reflecting the completeness and quality of the included studies, and the substantial differences seen in costs and QALYs between the SIRTs and current UK practice (including confidential PAS). The AG's analyses predicted lenvatinib to rank first in terms of NMB in all scenarios (excluding scenario 4), whereas sorafenib was a cost-effective alternative, producing more QALYs at a higher cost. There are a number of differences between the AG model and those presented by the companies, which primarily concern the issues highlighted in the critique of these models in *Chapter 5*, *Review of economic evidence submitted by companies*. Strengths of the AG model include (1) all available high-quality RCT data were used to model the outcomes of the most relevant patient population to UK practice, (2) analyses included all appropriate comparators, (3) independent modelling of the costs and outcomes of patients who receive work-up but were ineligible to receive SIRT and (4) preserved randomisation and greater internal consistency with regard to the use of subsequent and curative therapies.

Insurmountable limitations in the evidence base meant that the AG was unable to address the question of the cost-effectiveness of SIRT in patients with early or intermediate HCC. The evidence for TheraSphere and QuiremSpheres in advanced HCC was extremely limited, and a lack of head-to-head evidence prevented a meaningful comparison of SIR-Spheres, TheraSphere and QuiremSpheres with one another in terms of clinical effectiveness. This essentially limits this particular comparison to that of a cost-minimisation, with a full comparison of the cost-effectiveness of SIRT versus sorafenib and lenvatinib. Although it is therefore not possible to discern which of the SIRTs offers the best value for money, the increased cost of the QuiremSpheres work-up procedure meant that it was consistently positioned last by some way in terms of NMB. The structure of the AG model and a lack of supporting evidence on the comparative effectiveness of QuiremSpheres, however, meant that there were no means by which the concept of 'suboptimal SIRT', as proposed by Terumo,[104] could realistically be explored. This includes the ostensibly greater selectivity of QuiremScout, and any quantifiable improvement in treatment effect resulting from optimisation of patient selection.

Chapter 8 Assessment of factors relevant to the NHS and other parties

End-of-life considerations

In the early- and intermediate-HCC populations, life expectancy reported in the most recent European Society For Medical Oncology guidelines[155] is > 24 months, with reported expected survival of > 5 years in the early population and > 2.5 years in the intermediate population. There is insufficient reliable evidence to indicate whether or not SIRT provides an extension to life of > 3 months.

The NICE end-of-life supplementary advice[142] outlines that end-of-life criteria should be applied when both of the criteria below are satisfied:

- The treatment is indicated for patients with a short life expectancy, normally < 24 months.
- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment.

Undiscounted LYG predicted in the AG's base-case analysis are presented in *Table 38*. These indicate that normal life expectancy for patients ineligible for CTT is < 24 months, with expected mean survival of 14.72 months on lenvatinib and 15.49 months on sorafenib. This conclusion remains consistent irrespective of the subgroup considered or the choice of parametric model used to represent OS.

Regarding the criterion relating to > 3 months' life extension, the AG's base-case analysis suggests that SIRT is marginally inferior to both systemic therapies (sorafenib and lenvatinib), indicating that this criterion is not met. The results for the subgroup with no MVI similarly suggest that sorafenib produces marginally greater LYG than SIRT. In the low tumour burden/ALBI 1 subgroup, SIRTs are predicted to provide an extension to life of 2.11 months compared with sorafenib and 2.80 months compared with lenvatinib. These predicted survival gains, however, exclude potential gains from downstaging. In scenarios conducted in the low tumour burden/ALBI 1 subgroup that allow for downstaging, predicted survival gains increase to 4.61 months compared with sorafenib and 5.30 months compared with lenvatinib. These predicted gains are, however, subject to significant uncertainty owing to the small sample sizes and the fact that this is a post hoc subgroup analysis. There are also very significant uncertainties regarding the plausibility of downstaging patients in this population.

TABLE 38 Undiscounted survival estimates used in the AG model

	Survival estimates (months)					
	AG base case		Low tumour/ALBI 1 subgroup		MVI subgroup	
Treatment	No downstaging	With downstaging	No downstaging	With downstaging	No downstaging	With downstaging
Undiscounted LYG: lenvatinib	14.72	15.12	16.98	17.49	15.80	16.14
Undiscounted LYG: sorafenib	15.49	15.89	17.68	18.17	16.49	16.82
Incremental undiscounted LYG: SIRT vs. lenvatinib[a]	−0.95	0.11	2.80	5.30	−2.49	−1.51
Incremental undiscounted LYG: SIRT vs. sorafenib[a]	−1.73	−0.65	2.11	4.61	−3.18	−2.19

a Each SIRT is associated with the same number of life-years owing to assumed equal efficacy.

Chapter 9 Discussion

Statement of principal findings

Treatment options vary for patients with unresectable HCC according to the stage of the cancer and the underlying liver disease. The AG, therefore, considered three distinct unresectable HCC patient populations, defined with respect to the aim of therapy and eligibility for comparator treatments. These three populations were as follows: (1) patients eligible for transplant, (2) patients ineligible for transplant but eligible for CTT and (3) patients ineligible for CTT. These three populations largely correspond to early-, intermediate- and advanced-stage HCC.

There is a large body of evidence on the clinical effectiveness and safety of SIRT compared with sorafenib or TACE; seven RCTs, seven prospective comparative studies, five retrospective comparative studies and one non-comparative case series were included in the review of clinical effectiveness. However, only two studies were considered to have a low risk of bias, the SARAH[19] and SIRveNIB[21] RCTs, which both compared SIR-Spheres with sorafenib. These studies enrolled patients with locally advanced HCC not amenable to curative treatment modalities and ineligible for CTT; the evidence for the early- and intermediate-HCC populations was significantly more limited. Both RCTs found no significant difference in OS or PFS between SIR-Spheres and sorafenib, despite a statistically significantly greater tumour response rate in the SIR-Spheres arm of both trials. The SARAH trial[19] reported a significant difference between groups in HRQoL, favouring SIR-Spheres; however, the proportion of patients who completed the questionnaires was low. AEs, particularly grade ≥ 3 events, were more frequent in the sorafenib group in both trials. There are some concerns regarding the generalisability of the results of these two RCTs to the UK HCC population, particularly the SIRveNIB trial,[21] which was conducted in the Asia-Pacific region, where the aetiology and treatment of HCC differ from those in Europe.

The Sirtex company submission[102] selected a subgroup of patients from the SARAH trial[19] with $\leq 25\%$ tumour burden and preserved liver function, defined as having ALBI 1, for the base-case analysis in its economic analysis. Although results appeared more promising in this subgroup of patients with a better prognosis, the results of this post hoc subgroup analysis should be prospectively validated before being considered relevant for clinical practice.

In studies that directly compared the different SIRTs, patients with PVT appeared to have better survival outcomes with TheraSphere than with SIR-Spheres; however, this result was from a small retrospective comparative study rated as being at a high risk of bias and, therefore, may not be reliable. Other studies comparing TheraSphere with SIR-Spheres that were not restricted to patients with PVT had conflicting results. The only study that compared QuiremSpheres with SIR-Spheres and TheraSphere was provided by Terumo as an addendum to its submission.[104] Clinical outcomes appeared to be similar between treatment groups; however, this was a very small pilot study with several methodological limitations.

Three NMA models were produced to represent the three different populations of unresectable HCC patients described above. Both the NMA in patients eligible for transplant and the NMA in patients eligible for CTT were not conducted owing to the uncertainty of using SIRT for bridging to transplant and downstaging in the UK, and a lack of good-quality evidence in patients eligible for CTT.

The base-case NMA was conducted in adults with unresectable HCC who have Child–Pugh class A liver function and are ineligible for CTT. There were no meaningful differences in OS between SIR-Spheres, sorafenib and lenvatinib in the per-protocol or ITT populations. All treatments appeared

to have similar efficacy. There was only one low-quality retrospective study that directly compared TheraSphere with SIR-Spheres in the base-case population.[39] Adding this study as a sensitivity analysis had a substantial effect on the NMA results: TheraSphere showed a significant improvement in OS when compared with SIR-Spheres, sorafenib and lenvatinib. However, these results may be biased and unreliable as they rely on only one low-quality retrospective study.

The limitations in the effectiveness evidence had an important role in shaping the economic analysis and restricted the focus of the AG's economic analysis to the population ineligible for CTT; this was the only population for which there were reliable estimates of the comparative effectiveness of SIRT with comparator technologies. The structure of the AG's model was broadly similar to the structures of the models developed by BTG and Sirtex for this population and was designed around a decision tree and partitioned survival model. The decision tree was used to model the fact that some patients eligible to receive SIRT will fail the work-up procedure and will not receive SIRT treatment; in a scenario analysis, the decision tree was also used to allow a proportion of patients to go on to receive curative therapies. The partitioned survival model developed was based on three health states: PFS, progressive disease and death.

The results of the AG's base-case analysis (probabilistic analysis), which assumed equal efficacy across all three SIRTs, suggested that TheraSphere is cost saving relative to both SIR-Spheres and QuiremSpheres. However, the incremental costs between TheraSphere and SIR-Spheres are < £300 and result from the additional cost of angiography required as part of the SIR-Spheres administration procedure. Pairwise NMB, assuming a £30,000 WTP threshold, for SIR-Spheres compared with TheraSphere was, therefore, close to zero (–£182). QuiremSpheres is associated with an incremental cost of £6955 relative to TheraSphere (exclusive of PAS). Pairwise NMB between QuiremSpheres and TheraSphere in the AG's base case was –£6599, exclusive of PAS. In the analysis including the confidential PAS for QuiremScout, QuiremSpheres remained more costly than both TheraSphere and SIR-Spheres and, as such, the pairwise NMB remained negative (see *Appendix 17* for full results).

In a fully incremental analysis, exclusive of the PAS discounts available for QuiremScout, sorafenib, lenvatinib and regorafenib, lenvatinib was the most cost-effective therapy and dominated TheraSphere (the lowest-costing SIRT treatment). Predicted NMB for lenvatinib compared with TheraSphere was –£2154. In a pairwise comparison of sorafenib with TheraSphere, the ICER for sorafenib was £31,974 per QALY, with an estimated NMB of –£150 (implying that TheraSphere is cost-effective compared with sorafenib at a WTP threshold of £30,000). In a fully incremental analysis inclusive of all confidential PAS discounts, lenvatinib remained the most cost-effective therapy across all scenarios, and dominated all three SIRTs, generating greater health benefits at lower costs. In pairwise comparisons of sorafenib with each SIRT, sorafenib also dominated all three SIRTs. Lenvatinib remained the most cost-effective option across 15 of the 17 AG scenarios when PAS discounts were included.

The results of the scenario analyses presented at list price showed that SIRTs were more likely to be cost-effective in the low tumour burden and ALBI 1 subgroup of patients, and when downstaging was permitted. The results of analyses conducted including PAS discounts for QuiremScout, sorafenib, lenvatinib and regorafenib, however, showed that the results of the AG's economic analysis were robust to a range of alternative parameter values and assumptions, with a negative incremental NMB predicted for all SIRTs at a £30,000 WTP threshold (see *Appendix 17* for details).

The AG's economic analysis suggests that, although current life expectancy in patients ineligible for CTT is likely to be < 24 months, the predicted life extension generated by SIRT is likely to be < 3 months.

Strengths and limitations of the assessment

The key strengths of this assessment are as follows:

- The reviews of clinical effectiveness and cost-effectiveness were based on comprehensive searches of the literature, which were supplemented by data identified in recent systematic reviews of CTT treatments.
- The review of clinical effectiveness evidence included a detailed mapping and quality assessment of all comparative evidence on SIRT treatments across a range of alternative positions in the treatment pathway.
- The AG's economic evaluation includes a fully incremental analysis of the three SIRTs (SIR-Spheres, TheraSphere and QuiremSpheres) and relevant systemic therapies (sorafenib and lenvatinib) in patients with CTT-ineligible HCC.
- The AG appropriately accounts for the fact that some patients eligible for SIRT treatment will fail the work-up procedure and will not go on to receive SIRT. Importantly, it recognises that patients who fail work-up are different from patients who successfully receive SIRT and tend to have inferior progression and survival outcomes.
- The AG's economic analysis includes an exploratory analysis of two potentially plausible prospective subgroups: (1) low tumour burden/ALBI 1 and (2) no MVI.
- The AG's economic analysis includes an exploration of the impact of downstaging in CTT-ineligible patients. The AG economic analysis also avoids double-counting the outcomes of patients who are downstaged to curative therapies.

The main weaknesses of the assessment are largely a consequence of weaknesses and gaps in the clinical evidence base:

- There is very limited evidence on the comparative effectiveness of SIRT with CTT in patients with either early- or intermediate-stage HCC. The AG did not consider the identified clinical evidence sufficient to produce an economic analysis and, therefore, the presented independent economic assessment covers only part of the NICE scope. The BTG company submission included an economic analysis of downstaging in CTT-eligible patients, whereas Sirtex presented a cost-minimisation model. The limits of the clinical evidence supporting these analyses and uncertainties regarding the equivalence of SIRT and CTT in this population mean that these analyses may be of limited relevance for decision-making.
- The AG did not have access to IPD from the SIRveNIB trial;[21] instead, PFS and OS outcomes were replicated using a published algorithm. Although the precision of this replication is likely to be good, this process may have introduced a small loss of accuracy relative to the use of IPD directly. Furthermore, the lack of IPD meant that the SIRveNIB trial could not be included in scenario analyses exploring the low tumour burden/ALBI 1 and no-MVI subgroups.
- Lack of IPD for the REFLECT trial,[81] comparing lenvatinib with sorafenib, meant that there were limited options for including lenvatinib in the economic analysis and the modelled HRs were based on a subgroup that did not fully align with the population eligible for SIRT. Furthermore, the AG's base case makes the assumption of proportional hazards between lenvatinib and sorafenib despite some evidence presented in previous technology appraisals that this assumption may not hold.
- There was limited evidence on the relative effectiveness of TheraSphere compared with other SIRTs or systemic therapy, with the limited studies identified all rated as being at a high risk of bias.
- There is no evidence on the comparative effectiveness of QuiremSpheres, with the exception of one small, methodologically weak pilot study provided as a late addendum by Terumo.
- There is limited evidence on the long-term outcomes of patients who receive therapy with curative intent. The AG's analysis and the Sirtex model present data from a historical US cohort study; these data are now several years old and potentially reflect a broader population of patients with HCC.

Uncertainties

The main uncertainties associated with the appraisal are as follows:

- The comparative effectiveness of SIRT in patients eligible for transplant or eligible for CTTs, such as DEB-TACE, TACE and TAE, is highly uncertain, with identified evidence limited to a small number of mainly observational studies.
- The comparative effectiveness of alternative SIRT (SIR-Spheres, TheraSphere and QuiremSpheres) in all HCC populations is largely unknown. The limited evidence available suggests that TheraSphere may be superior to SIR-Spheres for advanced HCC with PVI. The identified evidence is, however, of very low quality and, therefore, it is unknown whether or not the observed effects are the result of confounding bias. There is also no evidence on the comparative effectiveness of QuiremSpheres with any therapy, other than a very small pilot study with several methodological limitations that was provided as an addendum. This is significant, as QuiremSpheres uses a different work-up procedure and different radioactive isotope and therefore it is plausible that QuiremSpheres may have differential effectiveness when compared with SIR-Spheres and TheraSphere.
- The Sirtex submission[102] puts forward a subgroup of patients with a low tumour burden and preserved liver function as a potential subgroup of patients who may benefit from treatment with SIR-Spheres. This subgroup was, however, not prespecified and the randomisation procedure did not stratify for these characteristics. The subgroup analysis is also based on very few patients. The extent of any benefits in this subgroup are, therefore, subject to considerable uncertainty and a confirmatory study would be required to be confident that the observed benefits are not spurious.
- The role of downstaging in a CTT-ineligible population is currently unclear. In the SARAH trial,[19] a small proportion of patients were successfully downstaged to curative therapies. Advice received by the AG from clinical experts, however, suggests that downstaging in this population is likely to be very rare, and it is unclear whether or not the SARAH trial is representative of UK practice in this regard.
- In the SARAH trial,[19] patients with bilobar HCC had each lobe treated in separate SIRT administrations to avoid the risk of REILD. The Sirtex submission, however, suggests that, in UK practice, patients with bilobar HCC would have both lobes treated simultaneously. The impact of sequential versus simultaneous treatment is largely unknown and it is not fully clear what practice would be adopted in the UK; advice received from the AG's clinical advisors, however, suggests that sequential treatment would be more likely to be used in the UK.
- There is currently only limited evidence on the comparative effectiveness of combination therapy (SIRT combined with a systemic therapy). The searches of trial registration databases completed as part of the clinical effectiveness review, however, identified that a large RCT, STOP-HCC,[74] is set to report shortly. This RCT compares TheraSphere plus sorafenib with sorafenib alone and will provide new evidence on this comparison.
- In the NHS, systemic therapies are recommended only for those with Child–Pugh class A liver function; thus, the current standard of care for those with Child–Pugh class B liver function is BSC. There is a potential place for SIRT in a Child–Pugh class B7 population, who were represented in in the SARAH[19] and SIRveNIB[21] trials. However, there is currently no direct evidence on the comparative effectiveness of SIRT with BSC in this population, and currently no means of comparing them indirectly.

Chapter 10 Conclusions

The existing evidence cannot provide decision-makers with clear guidance on the comparative effectiveness of treatments in early- and intermediate-stage HCC. All of the identified studies were rated as being at a high risk of bias and included highly heterogeneous populations, limiting the conclusions that can be drawn from these results. The results of individual studies varied considerably, with some showing that CTT was superior to SIRT and vice versa. However, the available evidence suggests that SIRT may be beneficial in this population, with moderate improvements in PFS and transplantation rates.

The very limited evidence on the effectiveness of SIRT in early- and intermediate-HCC patients means that the AG was not able to generate a meaningful analysis of the value of SIRT in these populations. The focus of the AG's economic assessment was therefore on the advanced-HCC population who are ineligible to receive CTT. In this population, two large randomised trials (SARAH[19] and SIRveNIB[21]) have assessed the comparative effectiveness of SIR-Spheres with sorafenib. The results of these trials show that SIRT has similar effectiveness to sorafenib; notably, these studies were not designed as non-inferiority or equivalence trials. The systematic review also identified further evidence from a large RCT of the comparative effectiveness of the alternative systemic therapy lenvatinib with sorafenib, as well as observational evidence on the comparative effectiveness of TheraSphere with SIR-Spheres. The results of these studies were combined in a NMA, which showed no meaningful differences in OS between SIR-Spheres, sorafenib and lenvatinib. TheraSphere showed a significant improvement in OS when compared with SIR-Spheres, sorafenib and lenvatinib. However, there were only two retrospective studies that directly compared TheraSphere and SIR-Spheres and both were rated as being at a high risk of bias. Therefore, there is considerable uncertainty regarding the efficacy of TheraSphere, and the AG elected to assume equal efficacy across each SIRT technology in its base-case analysis.

The AG's economic analysis showed that SIRTs are very unlikely to be cost-effective up to a threshold of £30,000 per QALY. The fully incremental analysis, including confidential PAS discounts, showed that lenvatinib was the most cost-effective therapy, dominating all three SIRTs (i.e. producing more QALYs at a lower cost). Pairwise comparisons of sorafenib with each SIRTs also showed that sorafenib dominated all three SIRTs. The results of DSA and scenarios analysis, considering a variety of alternative assumptions, including the modelling of two alternative subgroups (low tumour burden/ALBI 1 and no MVI), showed that the results of the AG's economic analysis were generally robust to alternative parameter values and assumptions.

The AG's economic analysis suggests that NICE's criteria[142] for life-extending therapies given at the end of life are not met for SIRT in the broad advanced population as they do not meet the required 3-month extension to life. In the low tumour burden/ALBI 1 subgroup, there is a possibility that SIRT treatments may meet this threshold. However, the ICER for the most cost-effective SIRT technology in this scenario remains > £50,000 when PAS discounts are considered.

Implications for service provision

In the event that SIRT was recommended for use in the NHS, the AG does not anticipate that any substantial changes to service provision would be required, as SIRT (SIR-Spheres and TheraSphere) is already routinely administered across a number of specialist liver units.

Suggested research priorities

As discussed above, no strong conclusions should be drawn in the early- and intermediate-HCC populations owing to considerable uncertainty in estimates of effectiveness and a high risk of bias. A priority for further research is, therefore, the conduct of studies in these populations. In designing any evaluations, careful consideration should be given to the recruited population, and, where possible, studies should avoid combining these heterogeneous populations as the aims of therapy and range of treatments available vary considerably. Careful consideration should also be given to the outcomes measured. Many studies reported on TTP, but this was rarely defined within the study report and there were concerns regarding whether or not these data had been properly analysed. Few studies also reported on downstaging outcomes; these potentially play an important role in determining patient outcomes and downstaging is increasingly becoming a realistic option for some patients with intermediate-stage HCC.

The low tumour burden and preserved liver function subgroup potentially represents a group of prospectively identifiable patients for whom SIRT may be beneficial when compared with sorafenib. However, the evidence in support of these observed benefits is weak, because the observed results are based on a post hoc analysis of the SARAH trial,[19] which included only a small proportion of the total number of recruited patients. Future work considering this subgroup may, therefore, be useful. Of priority would be a similar analysis of the results of the SIRveNIB trial;[21] this could not be undertaken as part of the current appraisal as IPD were unavailable. A confirmatory trial in this subgroup may also be desirable depending on the results of any analysis of the SIRveNIB trial.[21]

There is currently only very limited evidence on the comparative effectiveness of the three SIRTs with one another. Future randomised prospective studies evaluating the alternative SIRTs would, therefore, be useful.

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Data-sharing statement

This is a systematic review that includes published and confidential data supplied by the participating manufacturers. No primary data were created for this report. The majority of data used are as reported in the publications listed throughout this report. Further information can be obtained from the corresponding author.

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Appendix 1 Search strategies for clinical effectiveness and cost-effectiveness

The search strategies below were used to identify studies for the systematic reviews of the clinical effectiveness and cost-effectiveness of SIRT.

Database search strategies

MEDLINE all

Includes Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE.

Via Ovid (http://ovidsp.ovid.com/).

Date range searched: 1946 to 25 January 2019.

Date searched: 28 January 2019.

Records retrieved: 1790.

Search strategy

1. Carcinoma, Hepatocellular/ (77,414)
2. Liver Neoplasms/ (137,452)
3. ((liver or hepato$ or hepatic$) adj3 (carcinoma$ or cancer$ or neoplas$ or tumour$ or tumor$ or malign$)).ti,ab. (131,703)
4. hepatocarcinoma$.ti,ab. (3749)
5. hepatoma$.ti,ab. (27,351)
6. or/1-5 (207,214)
7. (Therasphere$ or Thera-sphere$).ti,ab. (66)
8. (SIR-Sphere$ or SIRSphere$).ti,ab. (100)
9. (QuiremSphere$ or Quirem-Sphere$).ti,ab. (0)
10. or/7-9 (142)
11. 6 and 10 (127)
12. Microspheres/ (27,127)
13. (microsphere$ or sphere$).ti,ab. (67,569)
14. (microbead$ or bead$).ti,ab. (49,738)
15. or/12-14 (123,972)
16. Yttrium Radioisotopes/ (2861)
17. Yttrium/ (2899)
18. Yttrium Isotopes/ (708)
19. (Yttrium$ or 90Yttrium$ or Y90 or Y-90 or 90Y or 90-Y).ti,ab. (8538)
20. Holmium/ (806)
21. (Holmium$ or 166Holmium$ or Ho-166 or Ho166 or 166Ho or 166-Ho).ti,ab. (2939)
22. Radiopharmaceuticals/ (47,137)
23. or/16-22 (60,317)
24. 15 and 23 (1616)
25. ((radioactiv$ or radio-activ$ or radionuclide$ or radio-nuclide$ or radioisotope$ or radio-isotope$ or radiolabel$ or radio-label$ or radiopharmaceutic$ or radio-pharmaceutic$) adj2 (sphere$ or microsphere$ or bead$ or microbead$)).ti,ab. (4140)

26. (radiomicrosphere$ or radio-microsphere$).ti,ab. (31)
27. or/24-26 (5660)
28. 6 and 27 (1020)
29. Brachytherapy/ (18,640)
30. (brachytherap$ or brachy-therap$ or microbrachytherap$).ti,ab. (16,214)
31. Embolization, Therapeutic/ (29,974)
32. or/29-31 (53,284)
33. 32 and (23 or 25 or 26) (1603)
34. 6 and 33 (815)
35. (radioemboli$ or radio-emboli$ or radioembolotherap$ or radio-embolotherap$).ti,ab. (1365)
36. TARE.ti,ab. (158)
37. (internal$ adj3 (radiation$ or radiotherap$ or radio therap$ or radionuclide$ or radio-nuclide$ or radioisotope$ or radio-isotope$)).ti,ab. (2182)
38. ((intra-arterial$ or intraarterial$) adj3 (radiation$ or radiotherap$ or radio therap$ or radionuclide$ or radio-nuclide$ or radioisotope$ or radio-isotope$)).ti,ab. (276)
39. ((intra-arterial$ or intraarterial$) adj2 (brachytherap$ or brachy-therap$)).ti,ab. (19)
40. SIRT.ti,ab. (1120)
41. (SIR adj2 (therap$ or treatment$)).ti,ab. (80)
42. (radiation adj2 (segmentectom$ or lobectom$)).ti,ab. (32)
43. or/35-42 (4675)
44. 6 and 43 (1675)
45. 11 or 28 or 34 or 44 (1978)
46. exp animals/not humans/ (4,541,052)
47. 45 not 46 (1915)
48. limit 47 to yr = "2000 -Current" (1790).

Key:

- / = indexing term [Medical Subject Heading (MeSH)]
- exp = exploded indexing term (MeSH)
- $ = truncation
- ti,ab = terms in either title or abstract fields
- adj3 = terms within three words of each other (any order).

EMBASE

Via Ovid (http://ovidsp.ovid.com/).

Date range searched: 1974 to 25 January 2019.

Date searched: 28 January 2019.

Records retrieved: 3440.

Search strategy

1. liver cell carcinoma/ (137,127)
2. liver cancer/ (28,908)
3. ((liver or hepato$ or hepatic$) adj3 (carcinoma$ or cancer$ or neoplas$ or tumour$ or tumor$ or malign$)).ti,ab. (185,054)
4. hepatocarcinoma$.ti,ab. (4972)
5. hepatoma$.ti,ab. (30,720)
6. or/1-5 (242,887)
7. (Therasphere$ or thera-sphere$).ti,ab,dv. (320)

8. (SIR-Sphere$ or SIRSphere$).ti,ab,dv. (479)
9. (QuiremSphere$ or Quirem-Sphere$).ti,ab,dv. (2)
10. brachytherapy device/ (555)
11. or/7-10 (1167)
12. 6 and 11 (487)
13. microsphere/ (28,744)
14. (microsphere$ or sphere$).ti,ab. (73,618)
15. (microbead$ or bead$).ti,ab. (71,652)
16. or/13-15 (148,521)
17. yttrium/ (4631)
18. yttrium 90/ (7567)
19. (Yttrium$ or 90Yttrium$ or Y90 or Y-90 or 90Y or 90-Y).ti,ab. (11,105)
20. holmium/ (1495)
21. (Holmium$ or 166Holmium$ or Ho-166 or Ho166 or 166Ho or 166-Ho).ti,ab. (4761)
22. radiopharmaceutical agent/ (26,611)
23. or/17-22 (46,979)
24. 16 and 23 (2924)
25. radioactive microsphere/ (937)
26. ((radioactiv$ or radio-activ$ or radionuclide$ or radio-nuclide$ or radioisotope$ or radio-isotope$ or radiolabel$ or radio-label$ or radiopharmaceutic$ or radio-pharmaceutic$) adj2 (sphere$ or microsphere$ or bead$ or microbead$)).ti,ab. (4430)
27. (radiomicrosphere$ or radio-microsphere$).ti,ab. (39)
28. or/24-27 (7517)
29. 6 and 28 (1922)
30. brachytherapy/ (34,809)
31. (brachytherap$ or brachy-therap$ or microbrachytherap$).ti,ab. (27,633)
32. artificial embolization/ (6954)
33. or/30-32 (44,694)
34. 33 and (23 or 25 or 26 or 27) (869)
35. 6 and 34 (221)
36. radioembolization/ (1554)
37. selective internal radiation.dq. (258)
38. intra arterial brachytherapy.dq. (1)
39. transarterial radioembolization.dq. (72)
40. (radioemboli$ or radio-emboli$ or radioembolotherap$ or radio-embolotherap$).ti,ab. (2887)
41. TARE.ti,ab. (416)
42. (internal$ adj3 (radiation$ or radiotherap$ or radio-therap$ or radionuclide$ or radio-nuclide$ or radioisotope$ or radio-isotope$)).ti,ab. (3166)
43. ((intra-arterial$ or intraarterial$) adj3 (radiation$ or radiotherap$ or radio-therap$ or radionuclide$ or radio-nuclide$ or radioisotope$ or radio-isotope$)).ti,ab. (363)
44. ((intra-arterial$ or intraarterial$) adj2 (brachytherap$ or brachy-therap$)).ti,ab. (18)
45. SIRT.ti,ab. (2238)
46. (SIR adj2 (therap$ or treatment$)).ti,ab. (185)
47. (radiation adj2 (segmentectom$ or lobectom$)).ti,ab. (77)
48. or/36-47 (8358)
49. 6 and 48 (3229)
50. 12 or 29 or 35 or 49 (3651)
51. (animal/or animal experiment/or animal model/or animal tissue/or nonhuman/) not exp human/ (5,653,185)
52. 50 not 51 (3560)
53. limit 52 to yr = “2000 -Current” (3440).

Key:

- / = indexing term (Emtree heading)
- exp = exploded indexing term (Emtree heading)
- $ = truncation
- ti,ab = terms in either title or abstract fields
- dv = terms in the device trade name field
- dq = terms in the candidate term word field
- adj3 = terms within three words of each other (any order).

Cumulative Index to Nursing and Allied Health Literature Plus

Via EBSCO*host* (www.ebscohost.com/).

Date range searched: inception to 28 January 2019.

Date searched: 28 January 2019.

Records retrieved: 724.

Search strategy

S1 (MH "Carcinoma, Hepatocellular") (7801)
S2 (MH "Liver Neoplasms") (12,189)
S3 TI ((liver or hepato* or hepatic*) N3 (carcinoma* or cancer* or neoplas* or tumour* or tumor* or malign*)) OR AB ((liver or hepato* or hepatic*) N3 (carcinoma* or cancer* or neoplas* or tumour* or tumor* or malign*)) (14,708)
S4 TI hepatocarcinoma* OR AB hepatocarcinoma* (173)
S5 TI hepatoma* OR AB hepatoma* (649)
S6 S1 OR S2 OR S3 OR S4 OR S5 (20,300)
S7 TI (Therasphere* or Thera-sphere*) OR AB (Therasphere* or Thera-sphere*) (19)
S8 TI (SIR-Sphere* or SIRSphere*) OR AB (SIR-Sphere* or SIRSphere*) (33)
S9 TI (QuiremSphere* or Quirem-Sphere*) OR AB (QuiremSphere* or Quirem-Sphere*) (0)
S10 S7 OR S8 OR S9 (46)
S11 S6 AND S10 (42)
S12 TI (microsphere* or sphere*) OR AB (microsphere* or sphere*) (3575)
S13 TI (microbead* or bead*) OR AB (microbead* or bead*) (2272)
S14 S12 OR S13 (5795)
S15 (MH "Radioisotopes") (3321)
S16 TI (Yttrium* or 90Yttrium* or Y90 or Y-90 or 90Y or 90-Y) OR AB (Yttrium* or 90Yttrium* or Y90 or Y-90 or 90Y or 90-Y) (1061)
S17 TI (Holmium* or 166Holmium* or Ho-166 or Ho166 or 166Ho or 166-Ho) OR AB (Holmium* or 166Holmium* or Ho-166 or Ho166 or 166Ho or 166-Ho) (281)
S18 (MH "Radiopharmaceuticals") (6050)
S19 S15 OR S16 OR S17 OR S18 (9807)
S20 S14 AND S19 (356)
S21 TI ((radioactiv* or radio-activ* or radionuclide* or radio-nuclide* or radioisotope* or radio-isotope* or radiolabel* or radio-label* or radiopharmaceutic* or radio-pharmaceutic*) N2 (sphere* or microsphere* or bead* or microbead*)) OR AB ((radioactiv* or radio-activ* or radionuclide* or radio-nuclide* or radioisotope* or radio-isotope* or radiolabel* or radio-label* or radiopharmaceutic* or radio-pharmaceutic*) N2 (sphere* or microsphere* or bead* or microbead*)) (104)
S22 TI (radiomicrosphere* or radio-microsphere*) OR AB (radiomicrosphere* or radio-microsphere*) (1)
S23 S20 OR S21 OR S22 (440)

S24 S6 AND S23 (261)
S25 (MH "Brachytherapy") (3045)
S26 TI (brachytherap* or brachy-therap* or microbrachytherap*) OR AB (brachytherap* or brachy-therap* or microbrachytherap*) (2956)
S27 (MH "Embolization, Therapeutic") (5975)
S28 S25 OR S26 OR S27 (10,145)
S29 S19 OR S21 OR S22 (9890)
S30 S28 AND S29 (603)
S31 S6 AND S30 (309)
S32 (MH "Radioembolization") (29)
S33 TI ((radioemboli* or radio-emboli* or radioembolotherap* or radio-embolotherap*) OR AB ((radioemboli* or radio-emboli* or radioembolotherap* or radio-embolotherap*) (654)
S34 TI TARE OR AB TARE (49)
S35 TI (internal* N3 (radiation* or radiotherap* or radio-therap* or radionuclide* or radio-nuclide* or radioisotope* or radio-isotope*)) OR AB (internal* N3 (radiation* or radiotherap* or radio-therap* or radionuclide* or radio-nuclide* or radioisotope* or radio-isotope*)) (327)
S36 TI ((intra-arterial* or intraarterial*) N3 (radiation* or radiotherap* or radio-therap* or radionuclide* or radio-nuclide* or radioisotope* or radio-isotope*)) OR AB ((intra-arterial* or intraarterial*) N3 (radiation* or radiotherap* or radio-therap* or radionuclide* or radio-nuclide* or radioisotope* or radio-isotope*)) (45)
S37 TI ((intra-arterial* or intraarterial*) N2 (brachytherap* or brachy-therap*)) OR AB ((intra-arterial* or intraarterial*) N2 (brachytherap* or brachy-therap*)) (5)
S38 TI SIRT OR AB SIRT (187)
S39 TI (SIR N2 (therap* or treatment*)) OR AB (SIR N2 (therap* or treatment*)) (37)
S40 TI (radiation N2 (segmentectom* or lobectom*)) OR AB (radiation N2 (segmentectom* or lobectom*)) (15)
S41 S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 (1140)
S42 S6 AND S41 (639)
S43 S11 OR S24 OR S31 OR S42 (727)
S44 TI (animal or animals or rat or rats or mouse or mice or rodent or rodents or porcine or murine or sheep or lamb or lambs or ewe or ewes or pig or pigs or piglet or piglets or sow or sows or minipig or minipigs or rabbit or rabbits or kitten or kittens or dog or dogs or puppy or puppies or monkey or monkeys or horse or horses or foal or foals or equine or calf or calves or cattle or heifer or heifers or hamster or hamsters or chicken or chickens or livestock or alpaca* or llama*) (87,260)
S45 S43 NOT S44 (724)
S46 S43 NOT S44
Limiters - Published Date: 20000101-20191231 (724).

Key:

- MH = indexing term (CINAHL heading)
- * = truncation
- TI = terms in the title
- AB = terms in the abstract
- N3 = terms within three words of each other (any order).

Science Citation Index

Via Web of Science, Clarivate Analytics (https://clarivate.com/).

Date range searched: 1900 to 25 January 2019.

Date searched: 28 January 2019.

Records retrieved: 2242.

Search strategy

38 2242 #35 NOT #36
Indexes=SCI-EXPANDED Timespan=2000-2019
37 2347 #35 NOT #36
36 2,811,336 TI=(animal or animals or rat or rats or mouse or mice or rodent or rodents or porcine or murine or sheep or lamb or lambs or ewe or ewes or pig or pigs or piglet or piglets or sow or sows or minipig or minipigs or rabbit or rabbits or kitten or kittens or dog or dogs or puppy or puppies or monkey or monkeys or horse or horses or foal or foals or equine or calf or calves or cattle or heifer or heifers or hamster or hamsters or chicken or chickens or livestock or alpaca* or llama*)
35 2419 #34 OR #24 OR #20 OR #9
34 2106 #33 AND #4
33 7874 #32 OR #31 OR #30 OR #29 OR #28 OR #27 OR #26 OR #25
32 48 TS=(radiation NEAR/2 (segmentectom* or lobectom*))
31 205 TS=(SIR NEAR/2 (therap* or treatment*))
30 1676 TS=SIRT
29 20 TS=((intra-arterial* or intraarterial*) NEAR/2 (brachytherap* or brachy-therap*))
28 289 TS=((intra-arterial* or intraarterial*) NEAR/3 (radiation* or radiotherap* or radio-therap* or radionuclide* or radio-nuclide* or radioisotope* or radio-isotope*))
27 3822 TS=(internal* NEAR/3 (radiation* or radiotherap* or radio-therap* or radionuclide* or radio-nuclide* or radioisotope* or radio-isotope*))
26 883 TS=TARE
25 2096 TS=(radioemboli* or radio-emboli* or radioembolotherap* or radio-embolotherap*)
24 263 #23 AND #4
23 533 #22 AND #21
22 47,345 #18 OR #17 OR #15
21 24,888 TS=(brachytherap* or brachy-therap*or microbrachytherap*)
20 1517 #19 AND #4
19 4871 #18 OR #17 OR #16
18 19 TS=(radiomicrosphere* or radio-microsphere*)
17 2262 TS=((radioactiv* or radio-activ* or radionuclide* or radio-nuclide* or radioisotope* or radio-isotope* or radiolabel* or radio-label* or radiopharmaceutic* or radio-pharmaceutic*) NEAR/2 (sphere* or microsphere* or bead* or microbead*))
16 2721 #15 AND #12
15 45,198 #14 OR #13
14 7124 TS=(Holmium* or 166Holmium* or Ho-166 or Ho166 or 166Ho or 166-Ho)
13 38,768 TS=(Yttrium* or 90Yttrium* or Y90 or Y-90 or 90Y or 90-Y)
12 310,417 #11 OR #10
11 81,252 TS=(microbead* or bead*)
10 235,358 TS=(microsphere* or sphere*)
9 216 #8 AND #4
8 283 #7 OR #6 OR #5
7 0 TS=(QuiremSphere* or Quirem-Sphere*)
6 172 TS=(SIR-Sphere* or SIRSphere*)
5 145 TS=(Therasphere* or Thera-sphere*)
4 199,180 #3 OR #2 OR #1
3 31,512 TS=(hepatoma*)
2 3551 TS=(hepatocarcinoma*)
1 173,805 TS=((liver or hepato* or hepatic*) NEAR/3 (carcinoma* or cancer* or neoplas* or tumour* or tumor* or malign*)).

Key:

- TS = topic tag; searches in title, abstract, author keywords and keywords plus fields
- TI = search in title field
- * = truncation
- NEAR/2 = terms within two words of each other (any order).

Cochrane Central Register of Controlled Trials

Via Wiley (http://onlinelibrary.wiley.com/).

Date range searched: issue 1 of 12, January 2019.

Date searched: 28 January 2019.

Records retrieved: 144.

The strategy below was used to search both the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews.

Search strategy

#1 MeSH descriptor: [Carcinoma, Hepatocellular] this term only (1483)
#2 MeSH descriptor: [Liver Neoplasms] this term only (2218)
#3 ((liver or hepato* or hepatic*) near/3 (carcinoma* or cancer* or neoplas* or tumour* or tumor* or malign*)):ti,ab,kw (6211)
#4 hepatocarcinoma*:ti,ab,kw (57)
#5 hepatoma*:ti,ab,kw (119)
#6 [OR #1-#5] (6287)
#7 (Therasphere* or Thera next sphere*):ti,ab,kw (9)
#8 (SIRSphere* or SIR next Sphere*):ti,ab,kw (43)
#9 (QuiremSphere* or Quirem next Sphere*):ti,ab,kw (0)
#10 [OR #7-#9] (52)
#11 #6 AND #10 (42)
#12 MeSH descriptor: [Microspheres] this term only (216)
#13 (microsphere* or sphere*):ti,ab,kw (1202)
#14 (microbead* or bead*):ti,ab,kw (948)
#15 [OR #12-#14] (2109)
#16 MeSH descriptor: [Yttrium Radioisotopes] this term only (78)
#17 MeSH descriptor: [Yttrium] this term only (123)
#18 MeSH descriptor: [Yttrium Isotopes] this term only (8)
#19 (Yttrium* or 90Yttrium* or “Y90” or “Y-90” or “90Y” or “90-Y”):ti,ab,kw (1147)
#20 MeSH descriptor: [Holmium] this term only (27)
#21 (Holmium* or 166Holmium* or “Ho-166” or “Ho166” or “166Ho” or “166-Ho”):ti,ab,kw (334)
#22 MeSH descriptor: [Radiopharmaceuticals] this term only (1425)
#23 [OR #16-#22] (2844)
#24 #15 AND #23 (117)
#25 ((radioactiv* or (radio next activ*) or radionuclide* or (radio next nuclide*) or radioisotope* or (radio next isotope*) or radiolabel* or (radio next label*) or radiopharmaceutic* or (radio next pharmaceutic*)) near/2 (sphere* or microsphere* or bead* or microbead*)):ti,ab,kw (15)
#26 (radiomicrosphere* or (radio next microsphere*)):ti,ab,kw (0)
#27 #24 OR #25 OR #26 (123)
#28 #6 AND #27 (94)
#29 MeSH descriptor: [Brachytherapy] this term only (653)

#30 (brachytherap* or brachy next therap* or microbrachytherap*):ti,ab,kw (1583)
#31 MeSH descriptor: [Embolization, Therapeutic] this term only (340)
#32 [OR #29-#31] (1919)
#33 #32 AND (#23 OR #25 OR #26) (46)
#34 #6 AND #33 (21)
#35 (radioemboli* or (radio next emboli*) or radioembolotherap* or (radio next embolotherap*)):ti,ab,kw (95)
#36 TARE:ti,ab,kw (105)
#37 (internal* near/3 (radiation* or radiotherap* or (radio next therap*) or radionuclide* or (radio next nuclide*) or radioisotope* or (radio next isotope*))):ti,ab,kw (116)
#38 ((intraarterial* or (intra next arterial)) near/3 (radiation* or radiotherap* or (radio next therap*) or radionuclide* or (radio next nuclide*) or radioisotope* or (radio next isotope*))):ti,ab,kw (17)
#39 ((intraarterial* or (intra next arterial*)) near/2 (brachytherap* or (brachy next therap*))):ti,ab,kw (2)
#40 SIRT:ti,ab,kw (99)
#41 (SIR near/2 (therap* or treatment*)):ti,ab,kw (10)
#42 (radiation near/2 (segmentectom* or lobectom*)):ti,ab,kw (1)
#43 [OR #35-#42] (336)
#44 #6 AND #43 (133)
#45 #11 OR #28 OR #34 OR #44 (150)
#46 #11 OR #28 OR #34 OR #44 with Cochrane Library publication date Between Jan 2000 and Jan 2019, in Cochrane Reviews, Cochrane Protocols (3)
#47 #11 OR #28 OR #34 OR #44 with Publication Year from 2000 to 2019, in Trials (144).

Key:

- MeSH descriptor = indexing term (MeSH)
- * = truncation
- ti,ab,kw = terms in either title or abstract or keyword fields
- near/3 = terms within three words of each other (any order)
- next = terms are next to each other.

Cochrane Database of Systematic Reviews

Via Wiley (http://onlinelibrary.wiley.com/).

Date range searched: issue 1 of 12, January 2019.

Date searched: 28 January 2019.

Records retrieved: 3.

See above under *Cochrane Central Register of Controlled Trials* for search strategy used.

Database of Abstracts of Reviews of Effects

URL: www.crd.york.ac.uk/CRDWeb/.

Date range searched: inception to 31 March 2015.

Date searched: 28 January 2019.

Records retrieved: 13.

The strategy below was used to search all three of the CRD databases: Database of Abstracts of Reviews of Effects, the HTA database and NHS EED.

Search strategy

1. MeSH DESCRIPTOR Carcinoma, Hepatocellular (385)
2. MeSH DESCRIPTOR Liver Neoplasms (567)
3. ((liver or hepato* or hepatic*) NEAR3 (carcinoma* or cancer* or neoplas* or tumour* or tumor* or malign*)) (850)
4. ((carcinoma* or cancer* or neoplas* or tumour* or tumor* or malign*) NEAR3 (liver or hepato* or hepatic*)) (587)
5. (hepatocarcinoma*) (8)
6. (hepatoma*) (7)
7. #1 OR #2 OR #3 OR #4 OR #5 OR #6 (891)
8. (Therasphere* or Thera-sphere*) (2)
9. (SIR-Sphere* or SIRSphere*) (5)
10. (QuiremSphere* or Quirem-Sphere*) (0)
11. #8 OR #9 OR #10 (5)
12. #7 AND #11 (4)
13. MeSH DESCRIPTOR Microspheres (16)
14. (microsphere* or sphere*) (44)
15. (micro-sphere* or sphere*) (16)
16. (microbead* or bead*) (34)
17. #13 OR #14 OR #15 OR #16 (74)
18. MeSH DESCRIPTOR Yttrium Radioisotopes (16)
19. MeSH DESCRIPTOR Yttrium (1)
20. MeSH DESCRIPTOR Yttrium Isotopes (0)
21. (Yttrium* or 90Yttrium* or Y90 or Y-90 or 90Y or 90-Y) (43)
22. MeSH DESCRIPTOR Holmium (9)
23. (Holmium* or 166Holmium* or Ho-166 or Ho166 or 166Ho or 166-Ho) (43)
24. MeSH DESCRIPTOR Radiopharmaceuticals (276)
25. #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 (350)
26. #17 AND #25 (10)
27. ((radioactiv* or radio-activ* or radionuclide* or radio-nuclide* or radioisotope* or radio-isotope* or radiolabel* or radio-label* or radiopharmaceutic* or radio-pharmaceutic*) NEAR2 (sphere* or microsphere* or bead* or microbead*)) (5)
28. ((sphere* or microsphere* or bead* or microbead*) NEAR2 (radioactiv* or radio-activ* or radionuclide* or radio-nuclide* or radioisotope* or radio-isotope* or radiolabel* or radio-label* or radiopharmaceutic* or radio-pharmaceutic*)) (3)
29. (radiomicrosphere* or radio-microsphere*) (0)
30. #26 OR #27 OR #28 OR #29 (11)
31. #7 AND #30 (11)
32. MeSH DESCRIPTOR Brachytherapy (133)
33. (brachytherap* or brachy-therap* or microbrachytherap*) (205)
34. MeSH DESCRIPTOR Embolization, Therapeutic (145)
35. #32 OR #33 OR #34 (348)
36. #25 OR #27 OR #28 (351)
37. #35 AND #36 (13)
38. #7 AND #37 (9)
39. (radioemboli* or radio-emboli* or radioembolotherap* or radio-embolotherap*) (17)
40. (TARE) (2)
41. (internal* NEAR3 (radiation* or radiotherap* or radio-therap* or radionuclide* or radio-nuclide* or radioisotope* or radio-isotope*)) (15)
42. ((radiation* or radiotherap* or radio-therap* or radionuclide* or radio-nuclide* or radioisotope* or radio-isotope*) NEAR3 internal*) (2)

43. ((intra-arterial* or intraarterial*) NEAR3 (radiation* or radiotherap* or radio-therap* or radionuclide* or radio-nuclide* or radioisotope* or radio-isotope*)) (0)
44. ((radiation* or radiotherap* or radio-therap* or radionuclide* or radio-nuclide* or radioisotope* or radio-isotope*) NEAR3 (intra-arterial* or intraarterial*)) (2)
45. ((intra-arterial* or intraarterial*) NEAR2 (brachytherap* or brachy-therap*)) (0)
46. ((brachytherap* or brachy-therap*) NEAR2 (intra-arterial* or intraarterial*)) (0)
47. (SIRT) (9)
48. (SIR NEAR2 (therap* or treatment*)) (0)
49. ((therap* or treatment*) NEAR2 SIR) (1)
50. (radiation NEAR2 (segmentectom* or lobectom*)) (0)
51. ((segmentectom* or lobectom*) NEAR2 radiation) (0)
52. #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 (34)
53. #7 AND #52 (25)
54. #12 OR #31 OR #38 OR #53 (29)

Key:

- MeSH DESCRIPTOR = indexing term (MeSH)
- * = truncation
- NEAR3 = terms within three words of each other (order specified).

Health Technology Assessment database

URL: www.crd.york.ac.uk/CRDWeb/.

Date range searched: inception to 31 March 2018.

Date searched: 28 January 2019.

Records retrieved: 14.

See above under *Database of Abstracts of Reviews of Effects* for search strategy used.

NHS Economic Evaluations Database

URL: www.crd.york.ac.uk/CRDWeb/.

Date range searched: inception to 31 March 2015.

Date searched: 28 January 2019.

Records retrieved: 2.

See above under *Database of Abstracts of Reviews of Effects* for search strategy used.

EconLit

Via Ovid (http://ovidsp.ovid.com/).

Date range searched: 1886 to 17 January 2019.

Date searched: 28 January 2019.

Records retrieved: 0.

Search strategy

1. ((liver or hepato$ or hepatic$) adj3 (carcinoma$ or cancer$ or neoplas$ or tumour$ or tumor$ or malign$)).ti,ab. (17)
2. hepatocarcinoma$.ti,ab. (0)
3. hepatoma$.ti,ab. (0)
4. or/1-3 (17)
5. (Therasphere$ or Thera-sphere$).ti,ab. (0)
6. (SIR-Sphere$ or SIRSphere$).ti,ab. (0)
7. (QuiremSphere$ or Quirem-Sphere$).ti,ab. (0)
8. 5 or 6 or 7 (0)
9. 4 and 8 (0)
10. (microsphere$ or sphere$).ti,ab. (2659)
11. (microbead$ or bead$).ti,ab. (12)
12. 10 or 11 (2671)
13. (Yttrium$ or 90Yttrium$ or Y90 or Y-90 or 90Y or 90-Y).ti,ab. (3)
14. (Holmium$ or 166Holmium$ or Ho-166 or Ho166 or 166Ho or 166-Ho).ti,ab. (1)
15. 13 or 14 (4)
16. 12 and 15 (0)
17. ((radioactiv$ or radio-activ$ or radionuclide$ or radio-nuclide$ or radioisotope$ or radio-isotope$ or radiolabel$ or radio-label$ or radiopharmaceutic$ or radio-pharmaceutic$) adj2 (sphere$ or microsphere$ or bead$ or microbead$)).ti,ab. (0)
18. (radiomicrosphere$ or radio-microsphere$).ti,ab. (0)
19. 16 or 17 or 18 (0)
20. 4 and 19 (0)
21. (brachytherap$ or brachy-therap$ or microbrachytherap$).ti,ab. (6)
22. 21 and (15 or 17 or 18) (0)
23. 4 and 22 (0)
24. (radioemboli$ or radio-emboli$ or radioembolotherap$ or radio-embolotherap$).ti,ab. (0)
25. TARE.ti,ab. (2)
26. (internal$ adj3 (radiation$ or radiotherap$ or radio therap$ or radionuclide$ or radio-nuclide$ or radioisotope$ or radio-isotope$)).ti,ab. (1)
27. ((intra-arterial$ or intraarterial$) adj3 (radiation$ or radiotherap$ or radio therap$ or radionuclide$ or radio-nuclide$ or radioisotope$ or radio-isotope$)).ti,ab. (0)
28. ((intra-arterial$ or intraarterial$) adj2 (brachytherap$ or brachy-therap$)).ti,ab. (0)
29. SIRT.ti,ab. (1)
30. (SIR adj2 (therap$ or treatment$)).ti,ab. (0)
31. (radiation adj2 (segmentectom$ or lobectom$)).ti,ab. (0)
32. or/24-31 (4)
33. 4 and 32 (0)
34. 9 or 20 or 23 or 33 (0).

Key:

- $ = truncation
- ti,ab = terms in either title or abstract fields
- adj3 = terms within three words of each other (any order).

Ongoing, unpublished or grey literature search strategies

ClinicalTrials.gov

URL: https://clinicaltrials.gov/.

Date searched: 1 February 2019.

Records retrieved: 157.

Advanced search screen used. Ten separate searches were used, retrieving 681 records in total, which were imported into EndNote X9 and deduplicated.

Search strategy

1. 93 studies found for: (Therasphere OR Thera-sphere OR SIR-Sphere OR SIRSphere OR QuiremSphere OR Quirem-Sphere) | (hepatocellular OR liver OR hepatic) AND (carcinoma OR cancer OR neoplasm OR tumour OR tumor OR malignancy)
2. 73 studies found for: (Therasphere OR Thera-sphere OR SIR-Sphere OR SIRSphere OR QuiremSphere OR Quirem-Sphere) | (hepatocarcinoma OR hepatoma)
3. 103 studies found for: (Microsphere OR sphere OR microbead OR bead) AND (Yttrium OR 90Yttrium OR Y90 OR Y-90 OR 90Y OR 90-Y OR Holmium OR 166Holmium OR Ho-166 OR Ho166 OR 166Ho OR 166-Ho) | (hepatocellular OR liver OR hepatic) AND (carcinoma OR cancer OR neoplasm OR tumour OR tumor OR malignancy)
4. 77 studies found for: (Microsphere OR sphere OR microbead OR bead) AND (Yttrium OR 90Yttrium OR Y90 OR Y-90 OR 90Y OR 90-Y OR Holmium OR 166Holmium OR Ho-166 OR Ho166 OR 166Ho OR 166-Ho) | (hepatocarcinoma OR hepatoma)
5. 38 studies found for: (brachytherapy OR brachy-therapy OR microbrachytherapy) AND (Yttrium OR 90Yttrium OR Y90 OR Y-90 OR 90Y OR 90-Y OR Holmium OR 166Holmium OR Ho-166 OR Ho166 OR 166Ho OR 166-Ho) | (hepatocellular OR liver OR hepatic) AND (carcinoma OR cancer OR neoplasm OR tumour OR tumor OR malignancy)
6. 26 studies found for: (brachytherapy OR brachy-therapy OR microbrachytherapy) AND (Yttrium OR 90Yttrium OR Y90 OR Y-90 OR 90Y OR 90-Y OR Holmium OR 166Holmium OR Ho-166 OR Ho166 OR 166Ho OR 166-Ho) | (hepatocarcinoma OR hepatoma)
7. 123 studies found for: (radioembolisation OR radioembolization OR radio-embolisation OR radio-embolization OR TARE OR SIRT OR SIR) | (hepatocellular OR liver OR hepatic) AND (carcinoma OR cancer OR neoplasm OR tumour OR tumor OR malignancy)
8. 94 studies found for: (radioembolisation OR radioembolization OR radio-embolisation OR radio-embolization OR TARE OR SIRT OR SIR) | (hepatocarcinoma OR hepatoma)
9. 32 studies found for: selective AND internal AND (radiation OR radiotherapy OR radio-therapy) | (hepatocellular OR liver OR hepatic) AND (carcinoma OR cancer OR neoplasm OR tumour OR tumor OR malignancy)
10. 22 studies found for: selective AND internal AND (radiation OR radiotherapy OR radio-therapy) | (hepatocarcinoma OR hepatoma)

World Health Organization International Clinical Trials Registry Platform

URL: www.who.int/ictrp/search/en/.

Date searched: 1 February 2019.

Records retrieved: 68.

Advanced search screen used. Ten separate searches were used, retrieving 103 records in total, which were imported into EndNote X9 and deduplicated.

Search strategy

1. Condition: hepatocellular carcinoma OR liver cancer AND Intervention: Therasphere OR Thera-sphere OR SIR-Sphere OR SIRSphere OR QuiremSphere OR Quirem-Sphere (11 hits)
2. Condition: hepatocarcinoma OR hepatoma AND Intervention: Therasphere OR Thera-sphere OR SIR-Sphere OR SIRSphere OR QuiremSphere OR Quirem-Sphere (4 hits)
3. Condition: hepatocellular carcinoma OR liver cancer AND Intervention: Microsphere OR sphere OR Yttrium OR 90Yttrium OR Y90 OR Y-90 OR 90Y OR 90-Y OR Holmium OR 166Holmium OR Ho-166 OR Ho166 OR 166Ho OR 166-Ho 45 records (37 trials)
4. Condition: hepatocarcinoma OR hepatoma AND Intervention: Microsphere OR sphere OR Yttrium OR 90Yttrium OR Y90 OR Y-90 OR 90Y OR 90-Y OR Holmium OR 166Holmium OR Ho-166 OR Ho166 OR 166Ho OR 166-Ho (6 hits)
5. Condition: hepatocellular carcinoma OR liver cancer AND Intervention: brachytherapy OR brachy-therapy OR microbrachytherapy (21 hits)
6. Condition: hepatocarcinoma OR hepatoma AND Intervention: brachytherapy OR brachy-therapy OR microbrachytherapy (6 hits)
7. Condition: hepatocellular carcinoma OR liver cancer AND Intervention: radioembolisation OR radioembolization OR radio-embolisation OR radio-embolization OR TARE OR SIRT OR SIR (23 records for 15 trials)
8. Condition: hepatocarcinoma OR hepatoma AND Intervention: radioembolisation OR radioembolization OR radio-embolisation OR radio-embolization OR TARE OR SIRT OR SIR (2 hits)
9. Condition: hepatocellular carcinoma OR liver cancer AND Intervention: selective internal radiation OR selective internal radiotherapy OR selective internal radio-therapy (1 hit)
10. Condition: hepatocarcinoma OR hepatoma AND Intervention: selective internal radiation OR selective internal radiotherapy OR selective internal radio-therapy (0 hits).

European Union Clinical Trials Register

URL: www.clinicaltrialsregister.eu/ctr-search/search.

Date searched: 1 February 2019.

Records retrieved: 62.

Search strategy

1. 3 result(s) found for: hepatocellular carcinoma AND (Therasphere OR Thera-sphere OR SIR-Sphere OR SIRSphere OR QuiremSphere OR Quirem-Sphere)
2. 3 result(s) found for: liver cancer AND (Therasphere OR Thera-sphere OR SIR-Sphere OR SIRSphere OR QuiremSphere OR Quirem-Sphere
3. 5 result(s) found for: hepatocellular carcinoma AND (Microsphere OR sphere OR Yttrium OR 90Yttrium OR Y90 OR Y-90 OR 90Y OR 90-Y OR Holmium OR 166Holmium OR Ho-166 OR Ho166 OR 166Ho OR 166-Ho)
4. 12 result(s) found for: liver cancer AND (Microsphere OR sphere OR Yttrium OR 90Yttrium OR Y90 OR Y-90 OR 90Y OR 90-Y OR Holmium OR 166Holmium OR Ho-166 OR Ho166 OR 166Ho OR 166-Ho)
5. 1 result(s) found for: hepatocellular carcinoma AND (brachytherapy OR brachy-therapy OR microbrachytherapy)
6. 7 result(s) found for: liver cancer AND (brachytherapy OR brachy-therapy OR microbrachytherapy)
7. 10 result(s) found for: hepatocellular carcinoma AND (radioembolisation OR radioembolization OR radio-embolisation OR radio-embolization OR TARE OR SIRT OR SIR)
8. 19 result(s) found for: liver cancer AND (radioembolisation OR radioembolization OR radio-embolisation OR radio-embolization OR TARE OR SIRT OR SIR)
9. 1 result(s) found for: hepatocellular carcinoma AND selective internal radiation
10. 1 result(s) found for: liver cancer AND selective internal radiation.

PROSPERO

URL: www.crd.york.ac.uk/PROSPERO/.

Date searched: 1 February 2019.

Records retrieved: 23.

Search strategy

#1 MeSH DESCRIPTOR Carcinoma, Hepatocellular (107)
#2 MeSH DESCRIPTOR Liver Neoplasms (158)
#3 (liver or hepato* or hepatic*) adj3 (carcinoma* or cancer* or neoplas* or tumour* or tumor* or malign*) (342)
#4 (carcinoma* or cancer* or neoplas* or tumour* or tumor* or malign*) ADJ3 (liver or hepato* or hepatic*) (206)
#5 hepatocarcinoma* (8)
#6 hepatoma* (11)
#7 #1 OR #2 OR #3 OR #4 OR #5 OR #6 (411)
#8 Therasphere* or Thera-sphere* (1)
#9 SIR-Sphere* or SIRSphere* (1)
#10 QuiremSphere* or Quirem-Sphere* (0)
#11 #8 OR #9 OR #10 (1)
#12 #11 AND #7 (1)
#13 MeSH DESCRIPTOR Microspheres (4)
#14 microsphere* or sphere* (87)
#15 microbead* or bead* (33)
#16 #13 OR #14 OR #15 (118)
#17 MeSH DESCRIPTOR Yttrium Radioisotopes (4)
#18 MeSH DESCRIPTOR Yttrium (3)
#19 MeSH DESCRIPTOR Yttrium Isotopes (0)
#20 Yttrium* or 90Yttrium* or Y90 or Y-90 or 90Y or 90-Y (13)
#21 MeSH DESCRIPTOR Holmium (1)
#22 Holmium* or 166Holmium* or Ho-166 or Ho166 or 166Ho or 166-Ho (11)
#23 MeSH DESCRIPTOR Radiopharmaceuticals (10)
#24 #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 (32)
#25 #24 AND #16 (6)
#26 (radioactiv* or radio-activ* or radionuclide* or radio-nuclide* or radioisotope* or radio-isotope* or radiolabel* or radio-label* or radiopharmaceutic* or radio-pharmaceutic*) adj2 (sphere* or microsphere* or bead* or microbead*) (0)
#27 (sphere* or microsphere* or bead* or microbead*) adj2 (radioactiv* or radio-activ* or radionuclide* or radio-nuclide* or radioisotope* or radio-isotope* or radiolabel* or radio-label* or radiopharmaceutic* or radio-pharmaceutic*) (0)
#28 radiomicrosphere* or radio-microsphere* (0)
#29 #26 OR #27 OR #28 (0)
#30 #25 OR #29 (6)
#31 #30 AND #7 (6)
#32 MeSH DESCRIPTOR Brachytherapy (14)
#33 brachytherap* or brachy-therap* or microbrachytherap* (76)
#34 MeSH DESCRIPTOR Embolization, Therapeutic (27)
#35 #32 OR #33 OR #34 (104)
#36 #24 OR #26 OR #27 OR #28 (32)
#37 #35 AND #36 (0)
#38 #37 AND #7 (0)

#39 radioemboli* or radio-emboli* or radioembolotherap* or radio-embolotherap* (14)
#40 TARE (10)
#41 internal* adj3 (radiation* or radiotherap* or radio therap* or radionuclide* or radio-nuclide* or radioisotope* or radio-isotope*) (10)
#42 (radiation* or radiotherap* or radio therap* or radionuclide* or radio-nuclide* or radioisotope* or radio-isotope*) adj3 internal* (3)
#43 (intra-arterial* or intraarterial*) adj3 (radiation* or radiotherap* or radio therap* or radionuclide* or radio-nuclide* or radioisotope* or radio-isotope*) (1)
#44 (radiation* or radiotherap* or radio therap* or radionuclide* or radio-nuclide* or radioisotope* or radio-isotope*) adj3 (intra-arterial* or intraarterial*) (3)
#45 (intra-arterial* or intraarterial*) adj2 (brachytherap* or brachy-therap*) (0)
#46 (brachytherap* or brachy-therap*) adj2 (intra-arterial* or intraarterial*) (0)
#47 SIRT (5)
#48 SIR adj2 (therap* or treatment*) (0)
#49 (therap* or treatment*) adj2 SIR (0)
#50 radiation adj2 (segmentectom* or lobectom*) (0)
#51 (segmentectom* or lobectom*) adj2 radiation (0)
#52 #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 (35)
#53 #52 AND #7 (23)
#54 #53 OR #38 OR #31 OR #12 (23).

Key:

- MeSH DESCRIPTOR = indexing term (MeSH)
- * = truncation
- adj3 = terms within three words of each other (order specified).

National Institute for Health and Care Excellence website

URL: www.nice.org.uk/.

Date searched: 8 May 2019.

Records retrieved: 6.

Search terms entered into main search box of the website:

1. 5 results for Therasphere OR Thera-sphere OR SIR-Sphere OR SIRSphere OR QuiremSphere OR Quirem-Sphere
2. 10 results for SIRT OR "SIR therapy" OR "SIR treatment" – browsed for any relevant to HCC – 3 results found
3. 5 results for radioembolisation OR radioembolization OR radioembolotherapy OR TARE - browsed for any relevant to HCC – 2 results found
4. 60 results found for hepatocellular carcinoma – browsed for any relevant to SIRT – 4 results found

Browsed the NICE guidance for liver cancers section of the website (www.nice.org.uk/guidance/conditions-and-diseases/cancer/liver-cancers): 3 results found relevant to SIRT.

The above search results were deduplicated, leaving six results in total retrieved from searches of this website.

NHS Evidence

URL: www.evidence.nhs.uk/.

Date searched: 8 May 2019.

Records retrieved: 18.

The following search strings were entered into the search box with the inbuilt guidance filters box checked to limit results to guidelines:

1. Therasphere OR "Thera sphere" OR "Thera-sphere" OR "SIR Sphere" OR "SIR-Sphere" OR SIRSphere OR QuiremSphere OR "Quirem Sphere" OR "Quirem-Sphere".

Two results.

2. "hepatocellular carcinoma" AND (SIRT OR "SIR therapy" OR "SIR treatment").

Nine results.

3. "hepatocellular carcinoma" AND (radioembolisation OR radioembolization OR radioembolotherapy OR TARE).

13 results.

4. "hepatocellular carcinoma" AND (microsphere OR yttrium or holmium).

12 results.

5. "hepatocellular carcinoma" AND (brachytherapy OR microbrachytherapy).

Four results.

The above search results were imported into EndNote X9 and deduplicated, leaving 18 results in total.

Conference Proceedings Citation Index – Science

Via Web of Science, Clarivate Analytics (https://clarivate.com/).

Date range searched: 1990 to 25 January 2019.

Date searched: 28 January 2019.

Records retrieved: 377.

Search strategy

38 (377) #35 not #36 Timespan=2000-2019
37 (391) #35 NOT #36
36 (257,731) TI=(animal or animals or rat or rats or mouse or mice or rodent or rodents or porcine or murine or sheep or lamb or lambs or ewe or ewes or pig or pigs or piglet or piglets or sow or sows or minipig or minipigs or rabbit or rabbits or kitten or kittens or dog or dogs or puppy

or puppies or monkey or monkeys or horse or horses or foal or foals or equine or calf or calves or cattle or heifer or heifers or hamster or hamsters or chicken or chickens or livestock or alpaca* or llama*)
35 (398) #34 OR #24 OR #20 OR #9
34 (316) #33 AND #4
33 (1585) #32 OR #31 OR #30 OR #29 OR #28 OR #27 OR #26 OR #25
32 (4) TS=(radiation NEAR/2 (segmentectom* or lobectom*))
31 (24) TS=(SIR NEAR/2 (therap* or treatment*))
30 (333) TS=SIRT
29 (4) TS=((intra-arterial* or intraarterial*) NEAR/2 (brachytherap* or brachy-therap*))
28 (52) TS=((intra-arterial* or intraarterial*) NEAR/3 (radiation* or radiotherap* or radio-therap* or radionuclide* or radio-nuclide* or radioisotope* or radio-isotope*))
27 (755) TS=(internal* NEAR/3 (radiation* or radiotherap* or radio-therap* or radionuclide* or radio-nuclide* or radioisotope* or radio-isotope*))
26 (180) TS=TARE
25 (357) TS=(radioemboli* or radio-emboli* or radioembolotherap* or radio-embolotherap*)
24 (11) #23 AND #4
23 (48) #22 AND #21
22 (8066) #18 OR #17 OR #15
21 (6589) TS=(brachytherap* or brachy-therap*or microbrachytherap*)
20 (193) #19 AND #4
19 (606) #18 OR #17 OR #16
18 (2) TS=(radiomicrosphere* or radio-microsphere*)
17 (153) TS=((radioactiv* or radio-activ* or radionuclide* or radio-nuclide* or radioisotope* or radio-isotope* or radiolabel* or radio-label* or radiopharmaceutic* or radio-pharmaceutic*) NEAR/2 (sphere* or microsphere* or bead* or microbead*))
16 (468) #15 AND #12
15 (7929) #14 OR #13
14 (1346) TS=(Holmium* or 166Holmium* or Ho-166 or Ho166 or 166Ho or 166-Ho)
13 (6670) TS=(Yttrium* or 90Yttrium* or Y90 or Y-90 or 90Y or 90-Y)
12 (44,967) #11 OR #10
11 (10,567) TS=(microbead* or bead*)
10 (34,955) TS=(microsphere* or sphere*)
9 (34) #8 AND #4
8 (56) #7 OR #6 OR #5
7 (0) TS=(QuiremSphere* or Quirem-Sphere*)
6 (29) TS=(SIR-Sphere* or SIRSphere*)
5 (30) TS=(Therasphere* or Thera-sphere*)
4 (22,436) #3 OR #2 OR #1
3 (1675) TS=(hepatoma*)
2 (305) TS=(hepatocarcinoma*)
1 (20,826) TS=((liver or hepato* or hepatic*) NEAR/3 (carcinoma* or cancer* or neoplas* or tumour* or tumor* or malign*)).

Key:

- TS = topic tag; searches terms in title, abstract, author keywords and keywords plus fields
- TI = search in title field
- * = truncation
- NEAR/3 = terms within three words of each other (any order).

ProQuest Dissertations & Theses A&I

Via ProQuest (www.proquest.com/).

Date searched: 28 January 2019.

Records retrieved: 25.

Six separate searches were run in this database, giving 38 hits in total, which were then imported into EndNote X9 for deduplication.

1. (TI,AB,IF(Therasphere* OR Thera-sphere*) OR TI,AB,IF(SIR-Sphere* OR SIRSphere*) OR TI,AB,IF (QuiremSphere* OR Quirem-Sphere*)) AND (TI,AB,IF((liver OR hepato* OR hepatic*) NEAR/3 (carcinoma* OR cancer* OR neoplas* OR tumour* OR tumor* OR malign*)) OR TI,AB,IF (hepatocarcinoma*) OR TI,AB,IF(hepatoma*)).

0 hits

2. (TI,AB,IF((liver OR hepato* OR hepatic*) NEAR/3 (carcinoma* OR cancer* OR neoplas* OR tumour* OR tumor* OR malign*)) OR TI,AB,IF(hepatocarcinoma*) OR TI,AB,IF(hepatoma*)) AND (((TI,AB,IF(microsphere* OR sphere*) OR TI,AB,IF(microbead* OR bead*)) AND (TI,AB,IF(Yttrium* OR 90Yttrium* OR Y90 OR Y-90 OR 90Y OR 90-Y) OR TI,AB,IF(Holmium* OR 166Holmium* OR Ho-166 OR Ho166 OR 166Ho OR 166-Ho))) OR TI,AB,IF((radioactiv* OR radio-activ* OR radionuclide* OR radio-nuclide* OR radioisotope* OR radio-isotope* OR radiolabel* OR radio-label* OR radiopharmaceutic* OR radio-pharmaceutic*) NEAR/2 (sphere* OR microsphere* OR bead* OR microbead*)) OR TI,AB,IF(radiomicrosphere* OR radio-microsphere*)) date limit 2000-2019.

15 hits

3. (TI,AB,IF(brachytherap* OR brachy-therap*or microbrachytherap*) AND ((TI,AB,IF(Yttrium* OR 90Yttrium* OR Y90 OR Y-90 OR 90Y OR 90-Y) OR TI,AB,IF(Holmium* OR 166Holmium* OR Ho-166 OR Ho166 OR 166Ho OR 166-Ho)) OR TI,AB,IF((radioactiv* OR radio-activ* OR radionuclide* OR radio-nuclide* OR radioisotope* OR radio-isotope* OR radiolabel* OR radio-label* OR radiopharmaceutic* OR radio-pharmaceutic*) NEAR/2 (sphere* OR microsphere* OR bead* OR microbead*)) OR TI,AB,IF(radiomicrosphere* OR radio-microsphere*))) AND (TI,AB,IF((liver OR hepato* OR hepatic*) NEAR/3 (carcinoma* OR cancer* OR neoplas* OR tumour* OR tumor* OR malign*)) OR TI,AB,IF(hepatocarcinoma*) OR TI,AB,IF(hepatoma*)) date limit 2000-2019.

One hit

4. (TI,AB,IF(radioemboli* OR radio-emboli* OR radioembolotherap* OR radio-embolotherap*) OR TI,AB,IF(TARE)) AND (TI,AB,IF((liver OR hepato* OR hepatic*) NEAR/3 (carcinoma* OR cancer* OR neoplas* OR tumour* OR tumor* OR malign*)) OR TI,AB,IF(hepatocarcinoma*) OR TI,AB,IF (hepatoma*)) date limit 2000-2019.

0 hits

5. (TI,AB,IF(internal* NEAR/3 (radiation* OR radiotherap* OR radio-therap* OR radionuclide* OR radio-nuclide* OR radioisotope* OR radio-isotope*)) OR TI,AB,IF((intra-arterial* OR intraarterial*) NEAR/3 (radiation* OR radiotherap* OR radio-therap* OR radionuclide* OR radio-nuclide* OR radioisotope* OR radio-isotope*))) AND (TI,AB,IF((liver OR hepato* OR hepatic*) NEAR/3 (carcinoma* OR cancer* OR neoplas* OR tumour* OR tumor* OR malign*)) OR TI,AB,IF(hepatocarcinoma*) OR TI,AB,IF(hepatoma*)) date limit 2000-2019.

12 hits

6. (TI,AB,IF((intra-arterial* OR intraarterial*) NEAR/2 (brachytherap* OR brachy-therap*)) OR TI,AB,IF(SIRT) OR TI,AB,IF(SIR NEAR/2 (therap* OR treatment*)) OR TI,AB,IF(radiation NEAR/2 (segmentectom* OR lobectom*))) AND (TI,AB,IF((liver OR hepato* OR hepatic*) NEAR/3 (carcinoma* OR cancer* OR neoplas* OR tumour* OR tumor* OR malign*)) OR TI,AB,IF(hepatocarcinoma*) OR TI,AB,IF(hepatoma*)) date limit 2000-2019.

10 hits

Key:

- TI,AB,IF = terms in title or abstract or keywords field.
- * = truncation
- NEAR/3 = terms within three words of each other (any order).

Appendix 2 Search strategies for comparator therapies

MEDLINE all

Includes Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE.

Via Ovid (http://ovidsp.ovid.com/).

Date range searched: 1946 to 3 May 2019.

Date searched: 7 May 2019.

Records retrieved: 449.

Lines 25–104 below are to limit the search to systematic reviews or meta-analyses, taken from a previous search strategy for finding reviews in MEDLINE developed by the CRD.[17] The strategy has been updated to include new MeSH terms and terminology relating to systematic reviews and NMA.

Search strategy

1. Carcinoma, Hepatocellular/ (78,688)
2. Liver Neoplasms/ (139,353)
3. ((liver or hepato$ or hepatic$) adj3 (carcinoma$ or cancer$ or neoplas$ or tumour$ or tumor$ or malign$)).ti,ab. (133,795)
4. hepatocarcinoma$.ti,ab. (3798)
5. hepatoma$.ti,ab. (27,491)
6. or/1-5 (209,848)
7. Chemoembolization, Therapeutic/ (5314)
8. (chemo-emboli$ or chemoemboli$).ti,ab. (7127)
9. (chemoembolotherap$ or chemo-embolotherap$).ti,ab. (4)
10. TACE.ti,ab. (4674)
11. cTACE.ti,ab. (87)
12. (DEBTACE or DEB-TACE).ti,ab. (157)
13. (eluting adj2 bead$).ti,ab. (500)
14. DC bead$.ti,ab. (95)
15. or/7-14 (9758)
16. 6 and 15 (7632)
17. Embolization, Therapeutic/ (30,350)
18. (embolization$ or embolisation$ or embolize$ or embolise$ or embolizing$ or embolising$ or embolotherap$).ti,ab. (46,678)
19. TAE.ti,ab. (2173)
20. or/17-19 (56,670)
21. 6 and 20 (6182)
22. ((locoregional or loco-regional) adj2 (therap$ or intervention$ or treatment$)).ti,ab. (2545)
23. 6 and 22 (914)
24. 16 or 21 or 23 (12,277)
25. “systematic review”/ (105,413)
26. systematic$ review$.ti,ab. (145,034)

27. meta-analysis as topic/ (16,900)
28. network meta-analysis/ (771)
29. meta-analytic$.ti,ab. (6484)
30. meta-analysis.ti,ab,pt. (150,374)
31. metanalysis.ti,ab. (186)
32. metaanalysis.ti,ab. (1505)
33. meta analysis.ti,ab. (125,205)
34. meta-synthesis.ti,ab. (731)
35. metasynthesis.ti,ab. (277)
36. meta synthesis.ti,ab. (731)
37. meta-regression.ti,ab. (6437)
38. metaregression.ti,ab. (577)
39. meta regression.ti,ab. (6437)
40. (synthes$ adj3 literature).ti,ab. (2958)
41. (synthes$ adj3 evidence).ti,ab. (8954)
42. integrative review.ti,ab. (2486)
43. data synthesis.ti,ab. (10,362)
44. (research synthesis or narrative synthesis).ti,ab. (2491)
45. (systematic study or systematic studies).ti,ab. (11,184)
46. (systematic comparison$ or systematic overview$).ti,ab. (3075)
47. evidence based review.ti,ab. (1870)
48. comprehensive review.ti,ab. (13,081)
49. critical review.ti,ab. (14,731)
50. quantitative review.ti,ab. (638)
51. structured review.ti,ab. (759)
52. realist review.ti,ab. (252)
53. realist synthesis.ti,ab. (173)
54. ((mixed or multiple or indirect) adj treatment$ comparison$).ti,ab. (672)
55. or/25-54 (310,742)
56. review.pt. (2,507,320)
57. medline.ab. (102,777)
58. pubmed.ab. (94,743)
59. cochrane.ab. (69,813)
60. embase.ab. (75,244)
61. cinahl.ab. (23,088)
62. psyc?lit.ab. (913)
63. psyc?info.ab. (28,630)
64. (literature adj3 search$).ab. (52,835)
65. (database$ adj3 search$).ab. (52,049)
66. (bibliographic adj3 search$).ab. (2270)
67. (electronic adj3 search$).ab. (19,250)
68. (electronic adj3 database$).ab. (25,028)
69. (computeri?ed adj3 search$).ab. (3402)
70. (internet adj3 search$).ab. (2953)
71. included studies.ab. (19,694)
72. (inclusion adj3 studies).ab. (14,219)
73. inclusion criteria.ab. (74,336)
74. selection criteria.ab. (28,289)
75. predefined criteria.ab. (1803)
76. predetermined criteria.ab. (1001)
77. (assess$ adj3 (quality or validity)).ab. (71,198)
78. (select$ adj3 (study or studies)).ab. (60,541)
79. (data adj3 extract$).ab. (55,029)

80. extracted data.ab. (12,670)
81. (data adj2 abstracted).ab. (4907)
82. (data adj3 abstraction).ab. (1520)
83. published intervention$.ab. (160)
84. ((study or studies) adj2 evaluat$).ab. (169,641)
85. (intervention$ adj2 evaluat$).ab. (10,195)
86. confidence interval$.ab. (373,846)
87. heterogeneity.ab. (149,380)
88. pooled.ab. (79,714)
89. pooling.ab. (11,224)
90. odds ratio$.ab. (244,194)
91. (Jadad or coding).ab. (169,547)
92. or/57-91 (1,312,289)
93. 56 and 92 (226,468)
94. review.ti. (419,930)
95. 94 and 92 (121,453)
96. (review$ adj4 (papers or trials or studies or evidence or intervention$ or evaluation$)).ti,ab. (169,610)
97. 55 or 93 or 95 or 96 (514,084)
98. letter.pt. (1,024,828)
99. editorial.pt. (488,807)
100. comment.pt. (769,090)
101. 98 or 99 or 100 (1,719,142)
102. 97 not 101 (502,003)
103. exp animals/not humans/ (4,576,104)
104. 102 not 103 (489,196)
105. 24 and 104 (587)
106. limit 105 to yr = "2010 -Current" (449).

Key:

- / = indexing term (MeSH)
- exp = exploded indexing term (MeSH)
- $ = truncation
- ? = optional wildcard – stands for zero or one character
- ti,ab = terms in either title or abstract fields
- adj3 = terms within three words of each other (any order)
- pt. = publication type.

EMBASE

Via Ovid (http://ovidsp.ovid.com/).

Date range searched: 1974 to 3 May 2019.

Date searched: 7 May 2019.

Records retrieved: 826.

Lines 26–122 below are to limit the search to systematic reviews or meta-analyses, taken from a previous search strategy for finding reviews in EMBASE developed by the CRD.[17] The strategy has been updated to include terminology relating to NMA.

Search strategy

1. liver cell carcinoma/ (139,370)
2. liver cancer/ (29,412)
3. ((liver or hepato$ or hepatic$) adj3 (carcinoma$ or cancer$ or neoplas$ or tumour$ or tumor$ or malign$)).ti,ab. (188,432)
4. hepatocarcinoma$.ti,ab. (5049)
5. hepatoma$.ti,ab. (30,865)
6. or/1-5 (246,579)
7. chemoembolization/ (14,765)
8. (chemo-emboli$ or chemoemboli$).ti,ab. (12,156)
9. (chemoembolotherap$ or chemo-embolotherap$).ti,ab. (6)
10. TACE.ti,ab. (9522)
11. cTACE.ti,ab. (242)
12. (DEBTACE or DEB-TACE).ti,ab. (563)
13. (eluting adj2 bead$).ti,ab,dq. (1254)
14. DC bead$.ti,ab. (291)
15. or/7-14 (20,050)
16. 6 and 15 (14,882)
17. artificial embolization/ (7551)
18. (embolization$ or embolisation$ or embolize$ or embolise$ or embolizing$ or embolising$ or embolotherap$).ti,ab. (68,834)
19. arterial embolization/ (2817)
20. TAE.ti,ab. (3247)
21. or/17-20 (72,488)
22. 6 and 21 (6603)
23. ((locoregional or loco-regional) adj2 (therap$ or intervention$ or treatment$)).ti,ab,dq. (4421)
24. 6 and 23 (1805)
25. 16 or 22 or 24 (19,749)
26. systematic$ review$.ti,ab. (179,774)
27. systematic$ literature review$.ti,ab. (13,292)
28. “systematic review”/ (201,979)
29. “systematic review (topic)”/ (23,396)
30. meta analysis/ (161,490)
31. “meta analysis (topic)”/ (39,538)
32. network meta-analysis/ (1756)
33. meta-analytic$.ti,ab. (7595)
34. meta-analysis.ti,ab. (162,787)
35. metanalysis.ti,ab. (506)
36. metaanalysis.ti,ab. (7350)
37. meta analysis.ti,ab. (162,787)
38. meta-synthesis.ti,ab. (789)
39. metasynthesis.ti,ab. (328)
40. meta synthesis.ti,ab. (789)
41. meta-regression.ti,ab. (7989)
42. metaregression.ti,ab. (948)
43. meta regression.ti,ab. (7989)
44. ((mixed or multiple or indirect) adj treatment$ comparison$).ti,ab. (1407)
45. (synthes$ adj3 literature).ti,ab. (3468)
46. (synthes$ adj3 evidence).ti,ab. (9985)
47. (synthes$ adj2 qualitative).ti,ab. (2510)
48. integrative review.ti,ab. (2400)
49. data synthesis.ti,ab. (12,440)

50. (research synthesis or narrative synthesis).ti,ab. (2765)
51. (systematic study or systematic studies).ti,ab. (11,923)
52. (systematic comparison$ or systematic overview$).ti,ab. (3381)
53. (systematic adj2 search$).ti,ab. (27,836)
54. systematic$ literature research$.ti,ab. (306)
55. (review adj3 scientific literature).ti,ab. (1709)
56. (literature review adj2 side effect$).ti,ab. (17)
57. (literature review adj2 adverse effect$).ti,ab. (3)
58. (literature review adj2 adverse event$).ti,ab. (15)
59. (evidence-based adj2 review).ti,ab. (3512)
60. comprehensive review.ti,ab. (15,039)
61. critical review.ti,ab. (15,755)
62. critical analysis.ti,ab. (7854)
63. quantitative review.ti,ab. (732)
64. structured review.ti,ab. (1026)
65. realist review.ti,ab. (267)
66. realist synthesis.ti,ab. (168)
67. (pooled adj2 analysis).ti,ab. (18,168)
68. (pooled data adj6 (studies or trials)).ti,ab. (2772)
69. (medline and (inclusion adj3 criteria)).ti,ab. (23,061)
70. (search adj (strateg$ or term$)).ti,ab. (34,448)
71. or/26-70 (501,726)
72. medline.ab. (127,052)
73. pubmed.ab. (120,450)
74. cochrane.ab. (90,230)
75. embase.ab. (95,039)
76. cinahl.ab. (26,915)
77. psyc?lit.ab. (992)
78. psyc?info.ab. (26,334)
79. lilacs.ab. (7057)
80. (literature adj3 search$).ab. (67,451)
81. (database$ adj3 search$).ab. (65,231)
82. (bibliographic adj3 search$).ab. (2672)
83. (electronic adj3 search$).ab. (23,469)
84. (electronic adj3 database$).ab. (33,807)
85. (computeri?ed adj3 search$).ab. (4093)
86. (internet adj3 search$).ab. (3981)
87. included studies.ab. (24,875)
88. (inclusion adj3 studies).ab. (17,595)
89. inclusion criteria.ab. (128,601)
90. selection criteria.ab. (33,810)
91. predefined criteria.ab. (2418)
92. predetermined criteria.ab. (1252)
93. (assess$ adj3 (quality or validity)).ab. (94,916)
94. (select$ adj3 (study or studies)).ab. (79,681)
95. (data adj3 extract$).ab. (75,259)
96. extracted data.ab. (16,453)
97. (data adj2 abstracted).ab. (8082)
98. (data adj3 abstraction).ab. (2225)
99. published intervention$.ab. (204)
100. ((study or studies) adj2 evaluat$).ab. (242,677)
101. (intervention$ adj2 evaluat$).ab. (14,361)
102. confidence interval$.ab. (448,335)

103. heterogeneity.ab. (190,795)
104. pooled.ab. (111,807)
105. pooling.ab. (14,826)
106. odds ratio$.ab. (306,423)
107. (Jadad or coding).ab. (200,705)
108. evidence-based.ti,ab. (130,860)
109. or/72-108 (1,828,351)
110. review.pt. (2,433,403)
111. 109 and 110 (227,600)
112. review.ti. (477,956)
113. 109 and 112 (151,152)
114. (review$ adj10 (papers or trials or trial data or studies or evidence or intervention$ or evaluation$ or outcome$ or findings)).ti,ab. (501,852)
115. (retriev$ adj10 (papers or trials or studies or evidence or intervention$ or evaluation$ or outcome$ or findings)).ti,ab. (26,856)
116. 71 or 111 or 113 or 114 or 115 (945,210)
117. letter.pt. (1,060,080)
118. editorial.pt. (598,624)
119. 117 or 118 (1,658,704)
120. 116 not 119 (927,165)
121. (animal/or nonhuman/) not exp human/ (5,382,670)
122. 120 not 121 (894,026)
123. 25 and 122 (1410)
124. limit 123 to yr = "2010 -Current" (1141)
125. limit 124 to conference abstracts (315)
126. 124 not 125 (826).

Key:

- / = indexing term (Emtree heading)
- exp = exploded indexing term (Emtree heading)
- $ = truncation
- ? = optional wildcard – stands for zero or one character
- ti,ab = terms in either title or abstract fields
- dq = terms in the candidate term word field
- adj3 = terms within three words of each other (any order)
- pt. = publication type.

Cochrane Database of Systematic Reviews

Via Wiley (http://onlinelibrary.wiley.com/).

Date range searched: issue 5 of 12, May 2019.

Date searched: 7 May 2019.

Records retrieved: 19.

Search strategy

#1 MeSH descriptor: [Carcinoma, Hepatocellular] this term only (1552)
#2 MeSH descriptor: [Liver Neoplasms] this term only (2259)

#3 ((liver or hepato* or hepatic*) near/3 (carcinoma* or cancer* or neoplas* or tumour* or tumor* or malign*)):ti,ab,kw (8211)
#4 hepatocarcinoma*:ti,ab,kw (74)
#5 hepatoma*:ti,ab,kw (141)
#6 [OR #1-#5] (8301)
#7 MeSH descriptor: [Chemoembolization, Therapeutic] this term only (289)
#8 (chemo next emboli* or chemoemboli*):ti,ab,kw (1252)
#9 (chemoembolotherap* or chemo next embolotherap*):ti,ab,kw (0)
#10 TACE:ti,ab,kw (991)
#11 cTACE:ti,ab,kw (35)
#12 (DEBTACE or DEB next TACE):ti,ab,kw (46)
#13 (eluting near/2 bead*):ti,ab,kw (100)
#14 DC next bead*:ti,ab,kw (32)
#15 [OR #7-#14] (1478)
#16 #6 and #15 (1332)
#17 MeSH descriptor: [Embolization, Therapeutic] this term only (345)
#18 (embolization* or embolisation* or embolize* or embolise* or embolizing* or embolising* or embolotherap*):ti,ab,kw (2276)
#19 TAE:ti,ab,kw (3688)
#20 [OR #17-#19] (5858)
#21 #6 and #20 (521)
#22 ((locoregional or loco next regional) near/2 (therap* or intervention* or treatment*)):ti,ab,kw (426)
#23 #6 and #22 (122)
#24 #16 or #21 or #23 (1641)
#25 #16 or #21 or #23 with Cochrane Library publication date Between Jan 2010 and May 2019, in Cochrane Reviews, Cochrane Protocols (19).

Key:

- MeSH descriptor = indexing term (MeSH)
- * = truncation
- ti,ab,kw = terms in either title or abstract or keyword fields
- near/3 = terms within three words of each other (any order)
- next = terms are next to each other.

Database of Abstracts of Reviews of Effects

Via www.crd.york.ac.uk/CRDWeb/.

Date range searched: inception to 31 March 2015.

Date searched: 7 May 2019.

Records retrieved: 78.

Search strategy

1. MeSH DESCRIPTOR Carcinoma, Hepatocellular IN DARE,HTA (316)
2. MeSH DESCRIPTOR Liver neoplasms IN DARE,HTA (459)
3. (((liver or hepato* or hepatic*) NEAR3 (carcinoma* or cancer* or neoplas* or tumour* or tumor* or malign*))) IN DARE, HTA (627)

4. ((carcinoma* or cancer* or neoplas* or tumour* or tumor* or malign*) NEAR3 (liver or hepato* or hepatic*)) IN DARE, HTA (457)
5. (hepatocarcinoma*) IN DARE, HTA (3)
6. (hepatoma*) IN DARE, HTA (3)
7. #1 OR #2 OR #3 OR #4 OR #5 OR #6 (652)
8. MeSH DESCRIPTOR Chemoembolization, Therapeutic IN DARE,HTA (74)
9. ((chemo-emboli* or chemoemboli*)) IN DARE, HTA (98)
10. (chemoembolotherap* or chemo-embolotherap*) IN DARE, HTA (0)
11. (TACE) IN DARE, HTA (23)
12. (cTACE) IN DARE, HTA (0)
13. (DEBTACE or DEB-TACE) IN DARE, HTA (2)
14. (eluting NEAR2 bead*) IN DARE, HTA (10)
15. (bead* NEAR2 eluting) IN DARE, HTA (0)
16. (DC bead*) IN DARE, HTA (3)
17. #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 (101)
18. #7 AND #17 (98)
19. MeSH DESCRIPTOR Embolization, Therapeutic IN DARE,HTA (106)
20. ((emboli* or embolotherap*)) IN DARE, HTA (759)
21. (TAE) IN DARE, HTA (12)
22. #19 OR #20 OR #21 (767)
23. #7 AND #22 (39)
24. ((locoregional or loco-regional) NEAR2 (therap* or intervention* or treatment*)) IN DARE, HTA (17)
25. ((therap* or intervention* or treatment*) NEAR2 (locoregional or loco-regional)) IN DARE, HTA (6)
26. #24 OR #25 (19)
27. #7 AND #26 (7)
28. #18 OR #23 OR #27 (119)
29. (#28) IN DARE, HTA FROM 2010 TO 2019 (96)
30. (#29) IN DARE (78)
31. (#29) IN HTA (18)

Key:

- MeSH DESCRIPTOR = indexing term (MeSH)
- * = truncation
- NEAR3 = terms within three words of each other (order specified).

Health Technology Assessment database

Via www.crd.york.ac.uk/CRDWeb/.

Date range searched: inception to 31 March 2018.

Date searched: 7 May 2019.

Records retrieved: 18.

See above under *Database of Abstracts of Reviews of Effects* for search strategy used.

PROSPERO

URL: www.crd.york.ac.uk/PROSPERO/.

Date searched: 7 May 2019.

Records retrieved: 63.

Search strategy

#1 MeSH DESCRIPTOR Carcinoma, Hepatocellular (119)
#2 MeSH DESCRIPTOR Liver Neoplasms (172)
#3 (liver or hepato* or hepatic*) adj3 (carcinoma* or cancer* or neoplas* or tumour* or tumor* or malign*) (378)
#4 (carcinoma* or cancer* or neoplas* or tumour* or tumor* or malign*) adj3 (liver or hepato* or hepatic*) (224)
#5 hepatocarcinoma* (9)
#6 hepatoma* (12)
#7 #1 OR #2 OR #3 OR #4 OR #5 OR #6 (452)
#8 MeSH DESCRIPTOR Liver Neoplasms EXPLODE ALL TREES (183)
#9 MeSH DESCRIPTOR Chemoembolization, Therapeutic (14)
#10 chemo-emboli* or chemoemboli* (47)
#11 chemoembolotherap* or chemo-embolotherap* (0)
#12 TACE (41)
#13 cTACE (1)
#14 DEBTACE or DEB-TACE (6)
#15 eluting adj2 bead* (7)
#16 bead* adj2 eluting (0)
#17 DC bead* (0)
#18 #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 (59)
#19 #18 AND #7 (54)
#20 #18 NOT #19 (5)
#21 MeSH DESCRIPTOR Chemoembolization, Therapeutic EXPLODE ALL TREES (14)
#22 MeSH DESCRIPTOR Embolization, Therapeutic (29)
#23 embolization* or embolisation* or embolize* or embolise* or embolizing* or embolising* or embolotherap* (173)
#24 TAE (64)
#25 #22 OR #23 OR #24 (238)
#26 #25 AND #7 (34)
#27 (locoregional or loco-regional) adj2 (therap* or intervention* or treatment*) (20)
#28 #27 AND #7 (6)
#29 #28 OR #26 OR #19 (63).

Key:

- MeSH DESCRIPTOR = indexing term (MeSH)
- * = truncation
- adj3 = terms within three words of each other (order specified).

Appendix 3 Search strategies for quality-of-life studies

The aim of the search was to identify published studies reporting utility estimates for patients with HCC or cirrhosis. A search strategy was developed in MEDLINE (Ovid), consisting of terms for HCC or cirrhosis combined with a study design search filter to restrict retrieval to health state utility studies.[156] Specific named instruments used to measure HRQoL in HCC patients were also included in the strategy. No language or date restrictions were applied to the searches. The MEDLINE strategy was translated to run appropriately on the other databases searched.

The following databases were searched in February 2019: MEDLINE all (Ovid), Cost-Effectiveness Analysis Registry, EMBASE (Ovid), HTA database (CRD databases), NHS EED (CRD databases) and ScHARRHUD database.

Search results were imported into EndNote X9 and deduplicated.

MEDLINE all

Via Ovid (http://ovidsp.ovid.com/).

Date range searched: 1946 to 25 February 2019.

Date searched: 26 February 2019.

Records retrieved: 1837.

A study design search filter developed by Arber *et al.*[156] designed to restrict retrieval to health state utility studies was included in the strategy. The sensitivity-maximising version of the filter was used; see lines 13–35 below.

Search strategy

1. Carcinoma, Hepatocellular/ (77,760)
2. Liver Neoplasms/ (137,948)
3. ((liver or hepato$ or hepatic$) adj3 (carcinoma$ or cancer$ or neoplas$ or tumour$ or tumor$ or malign$)).ti,ab. (132,386)
4. hepatocarcinoma$.ti,ab. (3764)
5. hepatoma$.ti,ab. (27,397)
6. or/1-5 (208,036)
7. exp Liver Cirrhosis/ (84,653)
8. (cirrhos$ or cirrhot$).ti,ab. (93,295)
9. ((liver or hepatic$) adj3 fibros$).ti,ab. (22,118)
10. (biliary adj3 (cirrhos$ or cirrhot$ or cholangitis)).ti,ab. (9992)
11. or/7-10 (132,914)
12. 6 or 11 (311,502)
13. quality-adjusted life years/ (10,727)
14. (quality adjusted or adjusted life year$).ti,ab,kf. (14,531)
15. (qaly$ or qald$ or qale$ or qtime$).ti,ab,kf. (9350)
16. (illness state$1 or health state$1).ti,ab,kf. (5828)
17. (hui or hui1 or hui2 or hui3).ti,ab,kf. (1350)

18. (multiattribute$ or multi attribute$).ti,ab,kf. (814)
19. (utility adj3 (score$1 or valu$ or health$ or cost$ or measur$ or disease$ or mean or gain or gains or index$)).ti,ab,kf. (13,429)
20. utilities.ti,ab,kf. (6374)
21. (eq-5d or eq5d or eq-5 or eq5 or euro qual or euroqual or euro qual5d or euroqual5d or euro qol or euroqol or euro qol5d or euroqol5d or euro quol or euroquol or euro quol5d or euroquol5d or eur qol or eurqol or eur qol5d or eur qol5d or eur?qul or eur?qul5d or euro$ quality of life or european qol).ti,ab,kf. (9564)
22. (euro$ adj3 (5 d or 5d or 5 dimension$ or 5dimension$ or 5 domain$ or 5domain$)).ti,ab,kf. (3329)
23. (sf36$ or sf 36$ or sf thirtysix or sf thirty six).ti,ab,kf. (20,320)
24. (time trade off$1 or time tradeoff$1 or tto or timetradeoff$1).ti,ab,kf. (1743)
25. quality of life/and ((quality of life or qol) adj (score$1 or measure$1)).ti,ab,kf. (10,526)
26. quality of life/and ec.fs. (9271)
27. quality of life/and (health adj3 status).ti,ab,kf. (8092)
28. (quality of life or qol).ti,ab,kf. and Cost-Benefit Analysis/ (11,091)
29. ((qol or hrqol or quality of life).ti,kf. or *quality of life/) and ((qol or hrqol$ or quality of life) adj2 (increas$ or decrease$ or improv$ or declin$ or reduc$ or high$ or low$ or effect or effects or worse or score or scores or change$1 or impact$1 or impacted or deteriorat$)).ab. (32,288)
30. Cost-Benefit Analysis/and (cost-effectiveness ratio$ and (perspective$ or life expectanc$)).ti,ab,kf. (2980)
31. *quality of life/and (quality of life or qol).ti. (48,595)
32. quality of life/and ((quality of life or qol) adj3 (improv$ or chang$)).ti,ab,kf. (23,881)
33. quality of life/and health-related quality of life.ti,ab,kf. (27,802)
34. models,economic/ (9191)
35. or/13-34 (146,623)
36. 12 and 35 (1437)
37. (utility adj3 (score$1 or scoring or valu$ or measur$ or evaluat$ or scale$1 or instrument$1 or weight or weights or weighting or information or data or unit or units or health$ or life or estimat$ or elicit$ or disease$ or mean or cost$ or expenditure$1 or gain or gains or loss or losses or lost or analysis or index$ or indices or overall or reported or calculat$ or range$ or increment$ or state or states or status)).ti,ab,kf. (29,854)
38. disutili$.ti,ab,kf. (405)
39. (short form$ or shortform$).ti,ab,kf. (29,550)
40. (sf12 or sf 12 or sf twelve or sftwelve).ti,ab,kf. (4154)
41. or/37-40 (61,362)
42. 12 and 41 (709)
43. 36 or 42 (1801)
44. “European Organization for Research and Treatment of Cancer Quality of Life”.ti,ab. (830)
45. “European Organisation for Research and Treatment of Cancer Quality of Life”.ti,ab. (336)
46. EORTC quality of life.ti,ab. (412)
47. (EORTC QLQ$ or EORTCQLQ$).ti,ab. (3173)
48. (QLQ-C30$ or QLQC30$ or QLQ-C-30$ or QLQC-30$).ti,ab. (3609)
49. (FACT-Hep or FACTHep).ti,ab. (35)
50. FACT-hepatobiliary.ti,ab. (10)
51. Functional Assessment of Cancer Therapy Hepatobiliary.ti,ab. (45)
52. (FHSI-8 or FHSI8).ti,ab. (6)
53. (FACT-G or FACTG).ti,ab. (554)
54. FACT-General.ti,ab. (69)
55. Functional Assessment of Cancer Therapy General.ti,ab. (452)
56. (QLQ-LC$ or QLQLC$).ti,ab. (114)
57. (QLQ-HCC18$ or QLQHCC18$ or QLQ-HCC-18$ or QLQHCC-18$).ti,ab. (11)
58. (QLQ-PAN$ or QLQPAN$).ti,ab. (40)
59. (Gastrointestinal Quality of Life adj (index$ or indices)).ti,ab. (387)

60. GIQLI$.ti,ab. (329)
61. or/44-60 (5833)
62. 12 and 61 (132)
63. 43 or 62 (1837).

Key:

- / = indexing term (MeSH)
- exp = exploded indexing term (MeSH)
- $ = truncation
- $1 = limited truncation – restricts to one character only after word
- ti,ab = terms in either title or abstract fields
- ec.fs. = floating economics subheading search
- kf = author keywords field
- adj3 = terms within three words of each other (any order).

Cost Effectivieness Analysis Registry

URL: http://healtheconomics.tuftsmedicalcenter.org/cear2n/search/search.aspx.

Date searched: 26 February 2019.

Records retrieved: 124.

The Cost-Effectiveness Analysis Registry was searched using the basic search interface using a set of simple searches for the population. Duplicates were removed before exporting records.

Search strategy

1. hepatocellular carcinoma (86)
2. hepatocellular cancer (1)
3. hepatocellular neoplasm (0)
4. hepatocellular tumor (0)
5. hepatocellular tumour (0)
6. hepatocellular malignancy (0)
7. hepatocarcinoma (0)
8. hepatoma (1)
9. liver cancer (12)
10. liver carcinoma (0)
11. liver neoplasm (6)
12. liver tumor (2)
13. liver tumour (1)
14. liver malignancy (0)
15. liver cirrhosis (21)
16. liver fibrosis (15).

EMBASE

Via Ovid (http://ovidsp.ovid.com/).

Date range searched: 1974 to 25 February 2019.

Date searched: 26 February 2019.

Records retrieved: 2415.

Retrieval was restricted to health state utility studies using terms based on a study design search filter developed by Arber *et al.*[156] for use in Ovid MEDLINE. This was translated for use in Ovid EMBASE; see lines 13–42 below.

1. liver cell carcinoma/ (136,695)
2. liver cancer/ (28,869)
3. ((liver or hepato$ or hepatic$) adj3 (carcinoma$ or cancer$ or neoplas$ or tumour$ or tumor$ or malign$)).ti,ab. (184,856)
4. hepatocarcinoma$.ti,ab. (4990)
5. hepatoma$.ti,ab. (30,679)
6. or/1-5 (242,352)
7. exp liver cirrhosis/ (141,130)
8. (cirrhos$ or cirrhot$).ti,ab. (135,400)
9. ((liver or hepatic$) adj3 fibros$).ti,ab. (36,133)
10. (biliary adj3 (cirrhos$ or cirrhot$ or cholangitis)).ti,ab. (13,554)
11. or/7-10 (194,904)
12. 6 or 11 (388,577)
13. quality adjusted life year/ (23,009)
14. (quality adjusted or adjusted life year$).ti,ab,kw. (21,303)
15. (qaly$ or qald$ or qale$ or qtime$).ti,ab,kw. (17,652)
16. (illness state$1 or health state$1).ti,ab,kw. (10,032)
17. (hui or hui1 or hui2 or hui3).ti,ab,kw. (2027)
18. (multiattribute$ or multi attribute$).ti,ab,kw. (1040)
19. (utility adj3 (score$1 or valu$ or health$ or cost$ or measur$ or disease$ or mean or gain or gains or index$)).ti,ab,kw. (21,358)
20. utilities.ti,ab,kw. (10,356)
21. (eq-5d or eq5d or eq-5 or eq5 or euro qual or euroqual or euro qual5d or euroqual5d or euro qol or euroqol or euro qol5d or euroqol5d or euro quol or euroquol or euro quol5d or euroquol5d or eur qol or eurqol or eur qol5d or eur qol5d or eur?qul or eur?qul5d or euro$ quality of life or european qol).ti,ab,kw. (17,622)
22. (euro$ adj3 (5 d or 5d or 5 dimension$ or 5dimension$ or 5 domain$ or 5domain$)).ti,ab,kw. (5144)
23. short form 36/ (24,680)
24. (sf36$ or sf 36$ or sf thirtysix or sf thirty six).ti,ab,kw. (34,476)
25. (time trade off$1 or time tradeoff$1 or tto or timetradeoff$1).ti,ab,kw. (2512)
26. quality of life/and ((quality of life or qol) adj (score$1 or measure$1)).ti,ab,kw. (22,209)
27. "quality of life"/and pe.fs. (8003)
28. "quality of life"/and de.fs. (300)
29. "quality of life"/and (health adj3 status).ti,ab,kw. (14,248)
30. (quality of life or qol).ti,ab,kw. and "cost benefit analysis"/ (5014)
31. ((qol or hrqol or quality of life).ti,kw. or *"quality of life"/) and ((qol or hrqol$ or quality of life) adj2 (increas$ or decrease$ or improv$ or declin$ or reduc$ or high$ or low$ or effect or effects or worse or score or scores or change$1 or impact$1 or impacted or deteriorat$)).ab. (49,462)
32. "cost benefit analysis"/and (cost-effectiveness ratio$ and (perspective$ or life expectanc$)).ti,ab,kw. (726)
33. *"quality of life"/and (quality of life or qol).ti. (74,391)
34. "quality of life"/and ((quality of life or qol) adj3 (improv$ or chang$)).ti,ab,kw. (65,833)
35. "quality of life"/and health-related quality of life.ti,ab,kw. (50,090)
36. economic model/ (1547)

37. (utility adj3 (score$1 or scoring or valu$ or measur$ or evaluat$ or scale$1 or instrument$1 or weight or weights or weighting or information or data or unit or units or health$ or life or estimat$ or elicit$ or disease$ or mean or cost$ or expenditure$1 or gain or gains or loss or losses or lost or analysis or index$ or indices or overall or reported or calculat$ or range$ or increment$ or state or states or status)).ti,ab,kw. (45,473)
38. disutili$.ti,ab,kw. (802)
39. (short form$ or shortform$).ti,ab,kw. (39,683)
40. short form 12/ (5132)
41. (sf12 or sf 12 or sf twelve or sftwelve).ti,ab,kw. (7154)
42. or/13-41 (294,270)
43. 12 and 42 (3994)
44. "European Organization for Research and Treatment of Cancer Quality of Life".ti,ab. (1083)
45. "European Organisation for Research and Treatment of Cancer Quality of Life".ti,ab. (445)
46. EORTC quality of life.ti,ab. (678)
47. (EORTC QLQ$ or EORTCQLQ$).ti,ab. (6855)
48. (QLQ-C30$ or QLQC30$ or QLQ-C-30$ or QLQC-30$).ti,ab. (7303)
49. (FACT-Hep or FACTHep).ti,ab. (88)
50. FACT-hepatobiliary.ti,ab. (21)
51. Functional Assessment of Cancer Therapy Hepatobiliary.ti,ab. (58)
52. (FHSI-8 or FHSI8).ti,ab. (14)
53. (FACT-G or FACTG).ti,ab. (1231)
54. FACT-General.ti,ab. (112)
55. Functional Assessment of Cancer Therapy General.ti,ab. (678)
56. (QLQ-LC$ or QLQLC$).ti,ab. (254)
57. (QLQ-HCC18$ or QLQHCC18$ or QLQ-HCC-18$ or QLQHCC-18$).ti,ab. (21)
58. (QLQ-PAN$ or QLQPAN$).ti,ab. (77)
59. (Gastrointestinal Quality of Life adj (index$ or indices)).ti,ab. (526)
60. GIQLI$.ti,ab. (550)
61. or/44-60 (11,272)
62. 12 and 61 (236)
63. 43 or 62 (4054)
64. (animal/or animal experiment/or animal model/or animal tissue/or nonhuman/) not exp human/ (5,661,185)
65. 63 not 64 (3979)
66. limit 65 to conference abstracts (1564)
67. 65 not 66 (2415).

Key:

- / = indexing term (Emtree heading)
- exp = exploded indexing term (Emtree heading)
- $ = truncation
- $1 = limited truncation – restricts to one character only after word
- ti,ab = terms in either title or abstract fields
- pe.fs = floating pharmacoeconomics subheading search
- de.fs = floating device economics subheading search
- kw = terms in the author keywords field
- adj3 = terms within three words of each other (any order).

Health Technology Assessment database

Via www.crd.york.ac.uk/CRDWeb/.

Date range searched: inception to 31 March 2018.

Date searched: 26 February 2019.

Records retrieved: 188.

Search strategy

1. MeSH DESCRIPTOR Carcinoma, Hepatocellular IN NHSEED,HTA (97)
2. MeSH DESCRIPTOR Liver Neoplasms IN NHSEED,HTA (174)
3. ((liver or hepato* or hepatic*) NEAR3 (carcinoma* or cancer* or neoplas* or tumour* or tumor* or malign*)) IN NHSEED, HTA (343)
4. ((carcinoma* or cancer* or neoplas* or tumour* or tumor* or malign*) NEAR3 (liver or hepato* or hepatic*)) IN NHSEED, HTA (202)
5. (hepatocarcinoma*) IN NHSEED, HTA (8)
6. (hepatoma*) IN NHSEED, HTA (5)
7. #1 OR #2 OR #3 OR #4 OR #5 OR #6 (365)
8. MeSH DESCRIPTOR Liver Cirrhosis EXPLODE ALL TREES IN NHSEED,HTA (129)
9. (cirrhos* or cirrhot*) IN NHSEED, HTA (340)
10. ((liver or hepatic*) NEAR3 fibros*) IN NHSEED, HTA (43)
11. (fibros* NEAR3 (liver or hepatic*)) IN NHSEED, HTA (11)
12. (biliary NEAR3 (cirrhos* or cirrhot* or cholangitis)) IN NHSEED, HTA (14)
13. ((cirrhos* or cirrhot* or cholangitis) NEAR3 biliary) IN NHSEED, HTA (8)
14. #8 OR #9 OR #10 OR #11 OR #12 OR #13 (350)
15. #7 OR #14 (540)
16. (#15) IN NHSEED (352)
17. (#15) IN HTA (188).

Key:

- MeSH DESCRIPTOR = indexing term (MeSH)
- * = truncation
- NEAR3 = terms within three words of each other (order specified).

NHS Economic Evaluations Database

Via www.crd.york.ac.uk/CRDWeb/.

Date range searched: inception to 31 March 2015.

Date searched: 26 February 2019.

Records retrieved: 352.

See above under *Health Technology Assessment database* for search strategy used.

ScHARRHUD

URL: www.scharrhud.org/.

Date searched: 26 February 2019.

Records retrieved: 11.

Search strategy

1. liver OR hepato* OR hepatic*
2. cirrhos* OR cirrhot*
3. biliary AND cholangitis
4. (#1 OR #2 OR #3).

Key:

- * = truncation.

Appendix 4 Search strategies for resource use and cost evidence

The aim of the search was to identify published studies relating to costs or resource use in patients with HCC. A search strategy was developed in MEDLINE (Ovid), comprising a set of terms for HCC combined with terms relating to costs or resource use. The terms included for costs were based on a search strategy developed by the Canadian Agency for Drugs and Technologies in Health (CADTH).[157] Retrieval was restricted to studies published from 2010 onwards in any language. The MEDLINE strategy was translated to run appropriately on the other databases searched.

The following databases were searched on 7 March 2019: MEDLINE all (Ovid) and EMBASE (Ovid). The previous results obtained for the health utilities search from the HTA database and NHS EED were added to the results from MEDLINE and EMBASE.

Search results were imported into EndNote X9 and deduplicated.

MEDLINE all

Via Ovid (http://ovidsp.ovid.com/).

Date range searched: 1946 to 6 March 2019.

Date searched: 7 March 2019.

Records retrieved: 2153.

Lines 7–19 below are based on a search strategy developed by CADTH to identify studies about costs/economics.[157]

Search strategy

1. Carcinoma, Hepatocellular/ (77,885)
2. Liver Neoplasms/ (138,136)
3. ((liver or hepato$ or hepatic$) adj3 (carcinoma$ or cancer$ or neoplas$ or tumour$ or tumor$ or malign$)).ti,ab. (132,179)
4. hepatocarcinoma$.ti,ab. (3767)
5. hepatoma$.ti,ab. (27,406)
6. or/1-5 (207,882)
7. economics/ (27,006)
8. exp “costs and cost analysis”/ (222,429)
9. economics, dental/ (1901)
10. exp “economics, hospital”/ (23,378)
11. economics, medical/ (9002)
12. economics, nursing/ (3986)
13. economics, pharmaceutical/ (2843)
14. exp “Fees and Charges”/ (29,616)
15. exp Budgets/ (13,465)
16. budget*.ti,ab,kf. (27,124)

17. (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kf. (209,622)
18. (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab./freq = 2 (258,034)
19. or/7-18 (523,885)
20. 6 and 19 (1325)
21. Health Resources/ (12,010)
22. Healthcare Financing/ (695)
23. (resource$ adj2 ("use" or utilis$ or utiliz$ or consum$ or usage)).ti,ab. (25,314)
24. ((healthcare or health-care) adj2 ("use" or utilis$ or utiliz$ or consum$ or usage)).ti,ab. (25,383)
25. 21 or 22 or 23 or 24 (56,988)
26. 6 and 25 (134)
27. Length of Stay/ (80,203)
28. (cost$ adj2 (illness$ or disease$ or sickness$)).ti,ab. (4600)
29. (burden$ adj2 (disease$ or illness$ or sickness$)).ti,ab. (22,257)
30. ((length or hospital$ or duration) adj2 stay$).ti,ab. (120,889)
31. ((extended or prolonged) adj stay$).ti,ab. (1013)
32. ((hospitali?ation$ or hospitali?ed) adj3 (economic$ or cost or costs or costly or costing or price or prices or pricing)).ti,ab. (6753)
33. economic consequenc$.ti,ab. (3229)
34. or/27-33 (190,256)
35. 6 and 34 (2349)
36. 20 or 26 or 35 (3467)
37. exp animals/not humans/ (4,553,712)
38. 36 not 37 (3454)
39. limit 38 to yr = "2010 -Current" (2153).

Key:

- / = indexing term (MeSH)
- exp = exploded indexing term (MeSH)
- $ = truncation
- ? = optional wild card – stands for zero or one character within a word
- ti,ab = terms in either title or abstract fields
- ab./freq = 2 = frequency operator – term must appear at least twice in the abstract for the record to be retrieved
- kf = author keywords field
- adj3 = terms within three words of each other (any order).

EMBASE

Via Ovid (http://ovidsp.ovid.com/).

Date range searched: 1974 to 6 March 2019.

Date searched: 7 March 2019.

Records retrieved: 3913.

Lines 7–14 below are based on a search strategy developed by CADTH to identify studies about costs/economics.[158]

Search strategy

1. liver cell carcinoma/ (136,950)
2. liver cancer/ (28,936)
3. ((liver or hepato$ or hepatic$) adj3 (carcinoma$ or cancer$ or neoplas$ or tumour$ or tumor$ or malign$)).ti,ab. (185,215)
4. hepatocarcinoma$.ti,ab. (5000)
5. hepatoma$.ti,ab. (30,696)
6. or/1-5 (242,760)
7. Economics/ (231,508)
8. Cost/ (56,142)
9. exp Health Economics/ (783,424)
10. Budget/ (26,815)
11. budget*.ti,ab,kw. (35,333)
12. (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kw. (253,689)
13. (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab./freq = 2 (357,407)
14. or/7-13 (1,153,032)
15. 6 and 14 (4962)
16. health care utilization/ (63,300)
17. health care financing/ (12,931)
18. (resource$ adj2 (“use” or utilis$ or utiliz$ or consum$ or usage)).ti,ab. (39,541)
19. ((healthcare or health-care) adj2 (“use” or utilis$ or utiliz$ or consum$ or usage)).ti,ab. (36,926)
20. 16 or 17 or 18 or 19 (122,638)
21. 6 and 20 (501)
22. disease burden/ (8049)
23. Length of Stay/ (159,340)
24. (cost$ adj2 (illness$ or disease$ or sickness$)).ti,ab. (6874)
25. (burden$ adj2 (disease$ or illness$ or sickness$)).ti,ab. (33,648)
26. ((length or hospital$ or duration) adj2 stay$).ti,ab. (204,289)
27. ((extended or prolonged) adj stay$).ti,ab. (1581)
28. ((hospitali?ation$ or hospitali?ed) adj3 (economic$ or cost or costs or costly or costing or price or prices or pricing)).ti,ab. (11,727)
29. economic consequenc$.ti,ab. (4245)
30. or/22-29 (313,622)
31. 6 and 30 (3966)
32. 15 or 21 or 31 (8470)
33. (animal/or animal experiment/or animal model/or animal tissue/or nonhuman/) not exp human/ (5,667,672)
34. 32 not 33 (8389)
35. limit 34 to yr = “2010 -Current” (6403)
36. limit 35 to conference abstracts (2490)
37. 35 not 36 (3913)

Key:

- / = indexing term (Emtree heading)
- exp = exploded indexing term (Emtree heading)
- $ = truncation
- ? = optional wild card – stands for zero or one character within a word

- ti,ab = terms in either title or abstract fields
- ab./freq = 2 = frequency operator – term must appear at least twice in the abstract for a record to be retrieved
- kw = terms in the author keywords field
- adj3 = terms within three words of each other (any order).

Health Technology Assessment database

Via www.crd.york.ac.uk/CRDWeb/.

Date range searched: inception to 31 March 2018.

Date searched: 26 February 2019.

Records retrieved: 188.

To view the search strategy, see under HRQoL search strategies in *Appendix 3*.

NHS Economic Evaluations Database

Via www.crd.york.ac.uk/CRDWeb/.

Date range searched: inception to 31 March 2015.

Date searched: 26 February 2019.

Records retrieved: 352.

To view the search strategy, see under HRQoL search strategies in *Appendix 3*.

Appendix 5 Risk-of-bias assessment results

Risk-of-bias assessment results for randomised controlled trials

Trial (first author and year)	Risk of bias arising from the randomisation process	Risk of bias owing to deviations from the intended interventions	Missing outcome data (primary outcome)	Risk of bias in measurement of the outcome	Risk of bias in selection of the reported result	Overall judgement of risk of bias
Vilgrain 2017[19,84]	Low	Low	Low	Low	Low	Low
SARAH						
Chow 2018[21]	Low	Low	Low	Low	Low	Low
SIRveNIB						
Kolligs 2015[22]	High	Low	High	High	Low	High
SIRTACE						
Pitton 2015[23]	Some concerns	Low	Low	Low	Low	Some concerns
Ricke 2015[24]	Some concerns	High	Low	Low	Low	High
SORAMIC						
Salem 2016[25–27]	High	Some concerns	Low	Low	Low	High
PREMIERE						
Kulik 2014[28–30]	Some concerns	Some concerns	Low	Some concerns	Low	Some concerns

Risk-of-bias assessment results for prospective comparative studies

Trial (first author and year)	Inclusion criteria clearly defined	Allocation to treatment groups adequately described/appropriate	Groups similar at baseline	Clearly described and consistently delivered intervention	Clearly described and consistently delivered comparator	Outcome assessors blinded	Missing outcome data balanced across groups	Free from suggestion of selective reporting	Overall judgement of risk of bias
Kirchner 2019[31]	No	No	No	Yes	No	No	Yes	Yes	High
El Fouly 2015[32]	Yes	No	No	Yes	Yes	No	Yes	Yes	High
Salem 2013[33]	Yes	No	No	Yes	Yes	No	Yes	Yes	High
Memon 2013[34]	Yes	No	Yes	Yes	Yes	No	Yes	Unclear	High
Hickey 2016[35]	Yes	No	No	Yes	Yes	No	Yes	Yes	High
Maccauro 2014[36]	No	No	Unclear	No	No	Unclear	Unclear	Unclear	High
Woodall 2009[37]	Yes	No	No	Yes	Yes	No	Yes	Yes	High

Risk-of-bias assessment results for retrospective comparative studies

Trial (first author and year)	Inclusion criteria clearly defined	Representative sample from relevant population	Groups similar at baseline	Clearly described and consistently delivered intervention	Clearly described and consistently delivered comparator	Outcome assessors blinded	Missing outcome data balanced across groups	Free from suggestion of selective reporting	Overall judgement of risk of bias
Biederman 2015[38]	No	Unclear	Unclear	No	No	Unclear	Unclear	Unclear	High
Biederman 2016[39]	Yes	Yes	No	Yes	Yes	Unclear	Unclear	Unclear	High
Van Der Gucht 2017[40]	Yes	Yes	No	Yes	Yes	Unclear	Yes	Yes	High
Bhangoo 2015[41]	Yes	Yes	Unclear	Yes	Yes	Unclear	Unclear	Yes	Unclear
d'Abadie 2018[42]	No	Unclear	No	No	No	Unclear	Unclear	Yes	High

Risk-of-bias assessment results for non-comparative studies

Trial (first author and year)	Inclusion criteria clearly defined	Representative sample from relevant population	Clearly described and consistently delivered intervention	Outcome measures prespecified, reliable and consistently assessed	Outcome assessors blinded	Attrition low and accounted for in analysis	Incomplete outcome data minimal/dealt with in analysis	Overall judgement of risk of bias
Radosa 2019[51]	Yes	Unclear	Yes	No	No	N/A (retrospective database of treated patients)	Yes	High

N/A, not applicable.

Appendix 6 Study details and results for all studies included in the systematic review of clinical effectiveness ($n = 20$)

Study (first author, year, name and location)	Study design and funding source	Population	Intervention	Comparator	Main results	Risk of bias
Vilgrain 2017[19,84] SARAH France	Multicentre open-label RCT Funding: Sirtex	Locally advanced HCC (BCLC C), or new HCC not eligible for surgery/ablation after previously cured HCC, or HCC with two unsuccessful rounds of TACE. Life expectancy of > 3 months, ECOG performance status of 0 or 1, Child–Pugh class A or B score of ≤ 7	SIR-Spheres ($n = 237$)	Sorafenib (400 mg twice daily orally, administered until the occurrence of radiological progression, unacceptable AEs or death) ($n = 222$)	**OS:** SIR-Spheres: median 8.0 months (95% CI 6.7 to 9.9 months); 196/237 (83%) patients died; 1-year OS: 39.5% (95% CI 33.3% to 45.9%) Sorafenib: median 9.9 months (95% CI 8.7 to 11.4 months); 177/222 (80%) patients died; 1-year OS: 42.1% (95% CI 35.6% to 48.7%) Comparison between groups: ITT population HR 1.15 (95% CI 0.94 to 1.41; $p = 0.18$) Per-protocol population HR 0.99 (95% CI 0.79 to 1.24) **PFS:** SIR-Spheres: median 4.1 months (95% CI 3.8 to 4.6 months); 218/237 (92%) had progression events Sorafenib: median 3.7 months (95% CI 3.3 to 5.4 months).; 205/222 (92%) had progression events Comparison between groups: ITT population HR 1.03 (95% CI 0.85 to 1.25; $p = 0.76$) **Complete or partial response rate:** SIR-Spheres: 36/190 (19%) evaluable patients Sorafenib: 23/198 (12%) evaluable patients	Low

Study (first author, year, name and location)	Study design and funding source	Population	Intervention	Comparator	Main results	Risk of bias
					HRQoL: The global health status subscore was significantly better in the SIRT group than in the sorafenib group (group effect $p = 0.0048$; time effect $p < 0.0001$) and the between- group difference tended to increase with time (group*time interaction $p = 0.0447$) for both the ITT and per-protocol populations **AEs:** SIR-Spheres: 173/226 (77%) patients reported at least one AE; 19 treatment-related deaths (six did not receive SIRT and subsequently received sorafenib) Sorafenib: 203/216 (94%) patients reported at least one AE; 12 treatment-related deaths; 139/216 (64%) patients discontinued sorafenib owing to drug-related toxicity, 108 of whom permanently discontinued **Time on treatment/number of treatments:** SIR-Spheres: 53/237 (22%) did not receive SIRT. Of 184 patients who received SIRT, 115 (63%) received a single administration, 58 patients received two treatments, 11 patients received three treatments Sorafenib: median dose intensity: 800 mg/day (IQR 585–800 mg/day). Median cumulative time of sorafenib intake 2.8 months (IQR 1.0–5.8 months); 82/216 (38%) required a dose reduction. Permanent discontinuation occurred in 132 (61%) patients; 49 (37%) patients discontinued sorafenib before tumour progression	

Study (first author, year, name and location)	Study design and funding source	Population	Intervention	Comparator	Main results	Risk of bias
Chow 2018[21] SIRveNIB Asia-Pacific region	Multicentre open-label RCT Funding: Sirtex	Locally advanced HCC (BCLC B or C without extrahepatic disease) with or without PVT, not amenable to curative treatment modalities	SIR-Spheres ($n = 182$)	Sorafenib (400 mg twice daily orally, administered until the occurrence of treatment failure, complete response, initiation of other HCC therapies, unacceptable AEs, patient request to stop treatment or death) ($n = 178$)	**OS:** SIR-Spheres: median 8.8 months (95% CI 7.5 to 10.8 months) Sorafenib: median 10.0 months (95% CI 8.6 to 13.8 months) Comparison between groups: ITT population HR 1.12 (95% CI 0.9 to 1.4; $p = 0.36$) Per-protocol population HR 0.86 (95% CI 0.7 to 1.1; $p = 0.27$) **PFS:** SIR-Spheres: median 5.8 months (95% CI 3.7 to 6.3 months) Sorafenib: median 5.1 months (95% CI 3.9 to 5.6 months) Comparison between groups: ITT population HR 0.89 (95% CI 0.7 to 1.1; $p = 0.31$)	Low

Study (first author, year, name and location)	Study design and funding source	Population	Intervention	Comparator	Main results	Risk of bias
					Complete or partial response rate: SIR-Spheres: 16.5% Sorafenib: 1.7% **HRQoL:** There were no statistically significant differences in the EQ-5D index between the SIR-Spheres and sorafenib groups throughout the study in either the ITT or the treated populations **AEs:** SIR-Spheres: 78/130 (60.0%) patients reported at least one AE; 36/130 (27.7%) reported at least one grade $\geq$ 3 AE; 27/130 (20.8%) reported at least one serious AE Sorafenib: 137/162 (84.6%) patients reported at least one AE; 82/130 (50.6%) reported at least one grade $\geq$ 3 AE; 57/162 (35.2%) reported at least one serious AE **Time on treatment/number of treatments:** SIR-Spheres: 52/182 (28.6%) did not receive SIRT. All 130 patients who received SIRT received a single administration Sorafenib: 16/178 (9%) did not receive sorafenib. Median treatment duration was 13.8 weeks and mean daily dose was 644.5 mg	

Study (first author, year, name and location)	Study design and funding source	Population	Intervention	Comparator	Main results	Risk of bias
Kolligs 2015[22] SIRTACE Germany and Spain	Multicentre open-label RCT Funding: Sirtex	Unresectable HCC with preserved liver function (Child–Pugh class $\leq$ B7; total bilirubin $\leq$ 2 mg/dl), an ECOG performance status of $\leq$ 2, and absence of any form of vascular invasion or extrahepatic spread	SIR-Spheres ($n = 13$)	TACE ($n = 15$)	**Overall survival:** Not reported **PFS:** SIR-Spheres: median 3.6 months (95% CI 2.3 to 6.2 months) TACE: median 3.7 months (95% CI 1.6 to 11.0 months) **Complete or partial response rate:** SIR-Spheres: 4/13 (30.8%) TACE: 2/15 (13.3%) **HRQoL:** HRQoL data were analysed for 18 patients (8 SIRT and 10 TACE). Higher scores reflect higher functioning and fewer symptoms. At baseline, median scores were lower for patients receiving SIRT than for patients receiving TACE, particularly for subscales of physical functioning (82.0 vs. 96.0; $p = 0.04$) by Kruskal–Wallis test This manifested in the lower scores with SIRT throughout the first 12 weeks after treatment, although the differences between the treatment groups by week 12 were not statistically significant for either FACT-Hep total or its subscales	High

Study (first author, year, name and location)	Study design and funding source	Population	Intervention	Comparator	Main results	Risk of bias
					AEs: SIR-Spheres: 12/13 (92.3%) patients reported at least one AE; 3/13 reported at least one grade ≥ 3 AE; 7/13 reported at least one serious AE requiring hospitalisation TACE: 10/15 (66.7%) patients reported at least one AE; 2/15 reported at least one grade ≥ 3 AE; 5/15 reported at least one serious AE requiring hospitalisation **Time on treatment/number of treatments:** SIR-Spheres: 7/13 (53.8%) received whole-liver SIRT, 5 (38.5%) received lobar and 1 (7.7%) received segmental treatment. All patients received one course of treatment TACE: on average, patients received 3.4 (SD 2.9, median 2.0) separate sessions during the study. three patients received one course of TACE, five patients received two courses, three patients received four courses, three patients received five courses and one patient received 11 courses	
Pitton 2015[23] Germany	Single-centre open-label RCT Funding: Johannes Gutenberg University of Mainz (Mainz, Germany)	Unresectable N0, M0 HCC (BCLC stage B)	SIR-Spheres ($n = 12$)	DEB-TACE ($n = 12$)	**OS:** SIR-Spheres: median 592 days (Q1: 192 days, Q3: –) Mean 437 days (SE 72 days). Cause of death was predominantly liver failure ($n = 4$), with only one death because of tumour progression DEB-TACE: median 788 days (Q1: 178 days, Q3: 950 days)	Some concerns

Study (first author, year, name and location)	Study design and funding source	Population	Intervention	Comparator	Main results	Risk of bias
					Mean 583 days (SE 119 days). Cause of death was predominantly tumour progression ($n = 4$), with only one death because of liver failure **PFS:** SIR-Spheres: median 180 days (Q1: 120 days, Q3: 414 days) Mean 266 days (SE 55 days) DEB-TACE: median 216 days (Q1: 88 days, Q3: 355 days) Mean 237 days (SE 49 days) **Complete or partial response rate:** Not reported **HRQoL:** Not reported **AEs:** Not reported **Time on treatment/number of treatments:** SIR-Spheres: patients received either one ($n = 4$) or two ($n = 8$) treatment sessions. Eight patients had a bilobar approach DEB-TACE: the mean number of treatment sessions was 3.8 ± 2.6 (range 1–10). Embolisation was unilobar in five and bilobar in seven patients	

Study (first author, year, name and location)	Study design and funding source	Population	Intervention	Comparator	Main results	Risk of bias
Ricke 2015[24] SORAMIC Germany	Multicentre open-label RCT Funding: Sirtex and Bayer HealthCare (Leverkusen, Germany)	Unresectable intermediate or advanced HCC (BCLC stage B or C) with preserved liver function (Child–Pugh class $\leq$ B7) and ECOG performance status of < 2, who were poor candidates for TACE (including those failing TACE)	SIR-Spheres plus sorafenib ($n = 20$)	Sorafenib alone ($n = 20$)	**OS:** Not reported **PFS:** Not reported **Complete or partial response rate:** Not reported **HRQoL:** Not reported **AEs:** SIR-Spheres plus sorafenib: there were 196 AEs reported; 43/196 (21.9%) were grade 3 or worse Sorafenib alone: there were 222 AEs reported; 47/222 (21.2%) were grade 3 or worse **Time on treatment/number of treatments:** SIR-Spheres plus sorafenib: SIRT was administered as a sequential lobar treatment in 10/20 patients, and 10 patients received unilobar treatment. Patients received a median daily sorafenib dose of 614 mg (range 45–793 mg) over a median of 8.5 months Sorafenib alone: patients received a median daily sorafenib dose of 557 mg (range 284–792 mg) over a median of 9.6 months	High

Study (first author, year, name and location)	Study design and funding source	Population	Intervention	Comparator	Main results	Risk of bias
Salem 2016[25–27] PREMIERE USA	Single-centre open-label RCT Funding: National Institutes of Health grant (in part)	BCLC stage A/B unablatable/ unresectable HCC with no vascular invasion. Child–Pugh class A/B	TheraSphere ($n = 24$)	TACE ($n = 21$)	**Overall survival:** TheraSphere: median 18.6 months (95% CI 7.4 to 32.5 months) TACE: median 17.7 months (95% CI 8.3 to not calcuable months) **TTP:** TheraSphere: not reached (> 26 months) TACE: 6.8 months **Complete or partial response rate:** TheraSphere: 20/23 (87%) achieved EASL response, 12/23 (52%) achieved WHO response TACE: 14/19 (74%) achieved EASL response, 12/19 (63%) achieved WHO response **HRQoL:** Not reported **AEs:** Not reported **Time on treatment/number of treatments:** TheraSphere: SIRT treatment was performed in 17/24 patients; seven were lobar treatments TACE: selective chemoembolisation was performed in 16/19 patients; three were lobar treatments	High

Study (first author, year, name and location)	Study design and funding source	Population	Intervention	Comparator	Main results	Risk of bias
Kulik 2014[28–30] USA	Single-centre open-label RCT pilot study Funding: Bayer/Onyx (Novato, CA, USA) and a Northwestern University (Evanston, IL, USA) departmental pilot grant programme	HCC, Child–Pugh class ≤ B8 and potential candidates for orthotopic liver transplantation	TheraSphere ($n = 10$)	TheraSphere plus sorafenib ($n = 10$)	**OS:** TheraSphere: three patients died TheraSphere plus sorafenib: two patients died **PFS:** Not reported **Complete or partial response rate:** Not reported **HRQoL:** Not reported **AEs:** The most commonly reported AEs were fatigue (9/10 TheraSphere patients and 4/10 TheraSphere plus sorafenib patients), pain (5/10 TheraSphere patients and 0 TheraSphere plus sorafenib patients) and nausea (7/10 TheraSphere patients and 2 TheraSphere plus sorafenib patients) **Time on treatment/number of treatments:** TheraSphere: 2/10 patients had more than one SIRT treatment; one patient had two SIRT treatments and one patient had three SIRT treatments plus one TACE TheraSphere plus sorafenib: 3/10 patients had more than one SIRT treatment; one patient had three SIRT treatments, one patient had a second SIRT treatment plus TACE and one patient had a second SIRT treatment plus radiofrequency ablation	Some concerns

Study (first author, year, name and location)	Study design and funding source	Population	Intervention	Comparator	Main results	Risk of bias
Kirchner 2019[31] Germany	Prospective single-centre comparative study Funding: none	All patients undergoing initial TACE or TARE due to HCC between November 2014 and March 2016 agreed to participate ($n = 94$). Twenty-seven patients failed to answer the questionnaire; therefore, quality of life after 67 interventions was analysed	TheraSphere ($n = 21$)	cTACE ($n = 33$) DEB-TACE ($n = 13$)	**OS:** Not reported **PFS:** Not reported **Complete or partial response rate (RECIST):** TheraSphere: 0/19 (0%) evaluable patients TACE: 1/44 (2.3%) evaluable patients **Complete or partial response rate (WHO):** TheraSphere: 1/19 (5.3%) evaluable patients TACE: 3/44 (6.8%) evaluable patients **HRQoL:** Before the intervention, the mean global health status/QoL in the SIRT group (50.8%) was significantly lower than in the TACE group (62.5%, $p = 0.029$) After treatment, the mean absolute decrease in global health status/QoL was higher in the TACE group (−10.5%) than in the SIRT group (−4.8%), which was not statistically significant ($p = 0.396$). The absolute increase in fatigue after initial treatment was significantly higher with TACE (+19.1%) than with SIRT (+7.9%) ($p = 0.021$)	High

Study (first author, year, name and location)	Study design and funding source	Population	Intervention	Comparator	Main results	Risk of bias
					The SIRT group showed the highest changes in financial difficulties (14.3% increase), role functioning (12.7% decrease) and dyspnoea (11.1% increase), C30 role functioning (12.7% decrease), social functioning (10.3% decrease) and QLQ-HCC18 nutrition (10.2% increase). The TACE group showed the highest changes in QOL-C30 physical functioning (14.1% decrease), role functioning (21.7% decrease), emotional functioning (10.2% decrease), social functioning (17.4% decrease) and fatigue (19.1% increase). It also showed an 11.6% increase in pain, QLQ-HCC18 fatigue (11.6% increase), body image (11.2% increase) and sex life (11.6% increase) Relative pre/post change in global health status was −16.8% in the TACE group and −9.4% in the SIRT group **AEs:** Not reported **Time on treatment/number of treatments:** Not reported	
El Fouly 2015[32] Germany and Egypt	Prospective multicentre comparative study Funding: not reported	Intermediate-stage (BCLC B) HCC and good liver function (Child–Pugh class B < 7)	TheraSphere ($n = 44$)	TACE ($n = 42$)	**OS:** TheraSphere: median 16.4 months (95% CI 7.9 to 25.3 months); 1-year OS: 59%, 2-year OS: 40%, 3-year OS: 31% TACE: median 18 months (95% CI 12.1 to 25.5 months); 1-year OS: 64%, 2-year OS: 36%, 3-year OS: 11%	High

Study (first author, year, name and location)	Study design and funding source	Population	Intervention	Comparator	Main results	Risk of bias
					TTP: TheraSphere: median 13.3 months (95% CI 3.4 to 23.1 months) TACE: median 6.8 months (95% CI 3.9 to 8.8 months) **Complete or partial response rate:** TheraSphere: 7% complete response, 68% partial response TACE: 5% complete response, 45% partial response **HRQoL:** Not reported **AEs:** The most commonly reported AE was unspecific abdominal pain, which was found in 83% of TACE patients (vs. 5% of SIRT patients) **Time on treatment/number of treatments:** TheraSphere: total number of sessions = 63, with a mean of 1.4 sessions per patient (median 1) TACE: total number of sessions = 93, with a mean of 2.2 sessions per patient (median 2 sessions)	

Study (first author, year, name and location)	Study design and funding source	Population	Intervention	Comparator	Main results	Risk of bias
Salem 2013[33] USA	Prospective comparative study Funding: Dimitrovich Family Foundation and National Institutes of Health (in part)	Treatment-naive HCC patients with ECOG performance status 0–2	TheraSphere ($n = 29$)	TACE ($n = 27$)	**OS:** Not reported **PFS:** Not reported **Complete or partial response rate:** Not reported **HRQoL:** Overall, most of the FACT-Hep scales showed a reduction in score in the TACE group, with stability or increase in the SIRT group between baseline and 4-week assessments Despite more advanced disease at baseline (regression analysis incorporating BCLC stage), SIRT patients showed significantly better quality of life relative to TACE in social well-being ($p = 0.019$), functional well-being ($p = 0.031$) and embolotherapy-specific score ($p = 0.018$). Strong trends favouring SIRT were noted in overall quality of life ($p = 0.055$), the Trial Outcome Index ($p = 0.05$) and FACT-Hep ($p = 0.071$) Differences in physical well-being, hepatobiliary cancer subscale and FACT-Hep were less pronounced. The only subscale that appeared to favour TACE was emotional well-being ($p = 0.656$) In terms of specific variables, 2 weeks after treatment, SIRT patients reported greater closeness to friends ($p = 0.035$), and TACE patients reported a greater feeling of sadness ($p = 0.034$). At 4 weeks, TACE patients	High

Study (first author, year, name and location)	Study design and funding source	Population	Intervention	Comparator	Main results	Risk of bias
					complained of being bothered by treatment side effects ($p = 0.029$) and nervousness ($p = 0.047$). SIRT patients experienced greater satisfaction with coping with illness ($p = 0.019$) and good appetite ($p = 0.045$) **AEs:** Not reported **Time on treatment/number of treatments:** Not reported	
Memon 2013[34] USA	Prospective follow-up to a retrospective comparative study Funding: National Institutes of Health (in part)	HCC that progressed after intra-arterial locoregional therapies: TACE and SIRT	TheraSphere ($n = 42$)	TACE ($n = 54$)	**OS:** Not reported **TTP:** TheraSphere: median 13.3 months (range 9.3–25.0 months) TACE: median 8.4 months (range 7.3–10.6 months) **Complete or partial response rate:** Not reported **HRQoL:** Not reported **AEs:** Not reported **Time on treatment/number of treatments:** Not reported	High

<table>
<tr><th>Study (first author, year, name and location)</th><th>Study design and funding source</th><th>Population</th><th>Intervention</th><th>Comparator</th><th>Main results</th><th>Risk of bias</th></tr>
<tr><td>Hickey 2016[35]

USA</td><td>Prospective single-centre comparative study

Funding: not reported</td><td>Unresectable HCC and bilirubin ≤ 3.0 mg/dl</td><td>TheraSphere (n = 428)</td><td>TACE (n = 337)</td><td>OS:

Survival outcomes (months) were stratified by Child–Pugh class and BCLC stage:

<table><tr><th></th><th>TheraSphere, median (95% CI)</th><th>TACE, median (95% CI)</th></tr><tr><td>BCLC A and Child–Pugh A</td><td>21.4 (9.8 to 33.1)</td><td rowspan="2">Not evaluable (most patients still alive at study termination)</td></tr><tr><td>BCLC A and Child–Pugh B</td><td>27.6 (11.6 to 43.6)</td></tr><tr><td>BCLC B and Child–Pugh A</td><td>18.3 (12.3 to 24.3)</td><td>19.2 (16.0 to 22.4)</td></tr><tr><td>BCLC B and Child–Pugh B</td><td>12.2 (8.1 to 16.3)</td><td>17.4 (8.8 to 26.0)</td></tr><tr><td>BCLC C and Child–Pugh A</td><td>9.5 (7.0 to 11.9)</td><td>8.6 (5.1 to 12.0)</td></tr><tr><td>BCLC C and Child–Pugh B</td><td>5.6 (4.1 to 7.1)</td><td>3.5 (2.6 to 4.4)</td></tr></table>
PFS:

Not reported

Complete or partial response rate:

Not reported

HRQoL:

Not reported</td><td>High</td></tr>
</table>

Study (first author, year, name and location)	Study design and funding source	Population	Intervention	Comparator	Main results	Risk of bias
					AEs: Not reported **Time on treatment/number of treatments:** Not reported	
Maccauro 2014[36] Location not reported	Prospective matched case–control study Funding: not reported	Unresectable HCC, Child–Pugh class A. 80% patients in both groups were BCLC stage C because of PVT	TheraSphere plus sorafenib ($n = 15$)	TheraSphere alone ($n = 30$)	**OS:** TheraSphere plus sorafenib: median 10 months TheraSphere alone: median 10 months **PFS:** TheraSphere plus sorafenib: median 6 months TheraSphere alone: median 7 months **Complete or partial response rate:** TheraSphere plus sorafenib: 45.5% mRECIST, 10% EASL TheraSphere alone: 42.8% mRECIST, 40% EASL **HRQoL:** Not reported **AEs:** Not reported	High

Study (first author, year, name and location)	Study design and funding source	Population	Intervention	Comparator	Main results	Risk of bias
					Time on treatment/number of treatments: TheraSphere plus sorafenib: patients started sorafenib at a median time of 2 months prior to SIRT; median time on sorafenib = 9 months and median dose = 600 mg/day	
Woodall 2009[37] USA	Prospective comparative study Funding: MDS Nordion (Ottawa, ON, Canada) (maker of TheraSphere)	Unresectable HCC, including patients with and those without PVT	TheraSphere in patients without PVT ($n = 20$) TheraSphere in patients with PVT ($n = 15$)	BSC/no treatment ($n = 17$)	**OS:** TheraSphere: HCC patients without PVT: median 13.9 months; HCC patients with PVT: median 3.2 months BSC/no treatment: median 5.2 months **PFS:** Not reported **Complete or partial response rate:** Not reported **HRQoL:** Not reported **AEs:** TheraSphere: AEs were reported by 25% of patients without PVT and 33% of patients with PVT **Time on treatment/number of treatments:** TheraSphere: median 2 treatments per patient (range 1–3)	High

Study (first author, year, name and location)	Study design and funding source	Population	Intervention	Comparator	Main results	Risk of bias
Biederman 2015[38] Location not reported	Retrospective comparative study Funding: not reported	BCLC stage C HCC with PVT	TheraSphere ($n = 72$)	SIR-Spheres ($n = 25$)	**OS:** TheraSphere: median 15 months (95% CI 8.6 to 19.5 months) SIR-Spheres: median 4.1 months (95% CI 2.7 to 6.6 months) **TTP:** Median 9.1 months (95% CI 5.4 to 11.7 months) – not reported for separate treatment groups **Complete or partial response rate:** 4/40 (10%) evaluable patients had complete response, 16/40 (40%) evaluable patients had partial response – not reported for separate treatment groups **HRQoL:** Not reported **AEs:** Clinical toxicities included grade 1/2: fatigue = 30%, abdominal pain = 28%, nausea = 17%, ascites = 7% – not reported for separate treatment groups Laboratory toxicities included grade 1/2: bilirubin = 37%, AST = 64%, ALT = 46% and grade 3/4: bilirubin = 17%, AST = 15%, ALT = 2% – not reported for separate treatment groups **Time on treatment/number of treatments:** A total of 101 treatments (across both treatment arms) were administered	High

Study (first author, year, name and location)	Study design and funding source	Population	Intervention	Comparator	Main results	Risk of bias
Biederman 2016[39] USA	Retrospective comparative study Funding: not reported	Unresectable HCC with associated main or lobar PVT	SIR-Spheres ($n = 21$)	TheraSphere ($n = 69$)	**OS:** SIR-Spheres: median 3.7 months (95% CI 2.3 to 6.0 months) TheraSphere: median 9.5 months (95% CI 7.6 to 15.0 months) Comparison between groups: HR 0.39 (95% CI 0.23 to 0.67, $p < 0.001$) **TTP:** SIR-Spheres: median 2.8 months (95% CI 1.9 to 4.3 months) TheraSphere: median 5.9 months (95% CI 4.2 to 9.1 months) **Complete or partial response rate:** SIR-Spheres: 0/15 (0%) evaluable patients had complete response, 2/15 (13.3%) had partial response, 4/15 (26.7%) had stable disease, 9/15 (60%) had progressive disease TheraSphere: 5/57 (8.8%) evaluable patients had complete response, 18/57 (31.6%) had partial response, 8/57 (14%) had stable disease, 26/57 (45.6%) had progressive disease **HRQoL:** Not reported	High

Study (first author, year, name and location)	Study design and funding source	Population	Intervention	Comparator	Main results	Risk of bias
					AEs: Grade 3/4 bilirubin: 39% SIR-Spheres vs. 14% TheraSphere group Grade 3/4 AST: 44% SIR-Spheres vs. 9% TheraSphere group Grade 3/4 ALT: 0% SIR-Spheres vs. 4% TheraSphere group Grade 3/4 alkaline phosphatase: 0% SIR-Spheres vs. 7% TheraSphere group Grade 3/4 albumin: 0% SIR-Spheres vs. 2% TheraSphere group Abdominal pain (32.9%) and fatigue (18.3%) were the most common clinical toxicities experienced; clinical toxicities were not significantly different between treatment groups Reported in supplementary data file (online): Pain: 41.2% SIR-Spheres vs. 30.8% TheraSphere group Fatigue: 17.6% SIR-Spheres vs. 18.5% TheraSphere group Nausea: 17.6% SIR-Spheres vs. 3.1% TheraSphere group Anorexia: 0% SIR-Spheres vs. 9.2% TheraSphere group	

Study (first author, year, name and location)	Study design and funding source	Population	Intervention	Comparator	Main results	Risk of bias
					Time on treatment/number of treatments: A total of 100 treatments (across both treatment arms) were administered, with 10 (11.1%) patients undergoing staged treatment	
Van Der Gucht 2017[40] Switzerland	Retrospective comparative study Funding: not reported	Unresectable HCC, ECOG performance status of < 2 and life expectancy of > 3 months	SIR-Spheres ($n = 41$)	TheraSphere ($n = 36$)	**OS:** SIR-Spheres: median 7.7 months (95% CI 7.2 to 8.2 months) OS at 6 months = 63%, 1 year = 22%, 2 years = 11% TheraSphere: median 7.0 months (95% CI 1.6 to 12.4 months) OS at 6 months = 57%, 1 year = 29%, 2 years = 14% **PFS:** SIR-Spheres: median 6.1 months (95% CI 4.7 to 7.4 months) PFS at 6 months = 52%, 1 year = 7%, 2 years = 0% TheraSphere: median 5.0 months (95% CI 0.9 to 9.2 months) PFS at 6 months = 47%, 1 year = 18%, 2 years = 6% **Complete or partial response rate:** Not reported	High

Study (first author, year, name and location)	Study design and funding source	Population	Intervention	Comparator	Main results	Risk of bias
					HRQoL: Not reported **AEs:** Not reported **Time on treatment/number of treatments:** Not reported	
Bhangoo 2015[41] USA	Retrospective comparative study Funding: not reported	Unresectable HCC patients who either had failed or had disease not amenable to alternative locoregional therapies. ECOG performance status of < 2, serum total bilirubin < 2 mg/dl	TheraSphere ($n = 11$)	SIR-Spheres ($n = 6$)	**OS:** TheraSphere: median 8.4 months (95% CI 1.3 to 21.1 months) SIR-Spheres: median 7.8 months (95% CI 2.3 to 12.5 months) OS results presented for 15 out of the full 17-patient cohort, as two patients still alive **PFS:** Not reported **Complete or partial response rate:** 0/17 patients had complete response, 4/17 (24%) had partial response, 4/17 (24%) had stable disease, 6/17 (35%) had progressive disease and 3/17 (18%) had no data – not reported for separate treatment groups **HRQoL:** Not reported	Unclear

Study (first author, year, name and location)	Study design and funding source	Population	Intervention	Comparator	Main results	Risk of bias
					AEs: Grade 3/4 bilirubin: 18% TheraSphere vs. 0% SIR-Spheres group Grade 3/4 albumin: 11% TheraSphere vs. 0% SIR-Spheres group Grade 3/4 alkaline phosphatase: 0% TheraSphere vs. 17% SIR-Spheres group Fatigue: 45% TheraSphere vs. 67% SIR-Spheres group Abdominal pain: 27% TheraSphere vs. 33% SIR-Spheres group Nausea/vomiting: 55% TheraSphere vs. 67% SIR-Spheres group Anorexia/weight loss: 9% TheraSphere vs. 33% SIR-Spheres group Diarrhoea: 0% TheraSphere vs. 17% SIR-Spheres group Gastric ulcer: 0% TheraSphere vs. 17% SIR-Spheres group **Time on treatment/number of treatments:** 65% of patients received one treatment and 35% received two treatments (across both treatment arms)	

Study (first author, year, name and location)	Study design and funding source	Population	Intervention	Comparator	Main results	Risk of bias
d'Abadie 2018[42] USA	Retrospective comparative study Funding: not reported	HCC imaged by yttrium-90 TOF-PET	TheraSphere ($n = 33$ procedures)	SIR-Spheres ($n = 25$ procedures)	**OS:** Not reported (KM curves for different equivalent uniform doses presented in publication) **PFS:** Not reported **Complete or partial response rate:** Not reported **HRQoL:** Not reported **AEs:** Not reported **Time on treatment/number of treatments:** Not reported	High
Radosa 2019[51] Germany	Single-centre retrospective case series Funding: none	HCC	QuiremSpheres ($n = 9$)	Not applicable	**OS:** Not reported **PFS:** Not reported	High

Study (first author, year, name and location)	Study design and funding source	Population	Intervention	Comparator	Main results	Risk of bias
					Complete or partial response rate: 60 days: 0 complete response, 5/9 (56%) partial response, 3/9 (33%) stable disease, 1/9 (11%) progressive disease 6 months: 1/9 (11%) complete response, 4/9 (45%) partial response, 3/9 (33%) stable disease, 1/9 (11%) progressive disease **HRQoL:** Not reported **AEs:** Presence of REILD at 60 days: 0 Median MELD score (range) 1 day before SIRT: 8 (7–13) Median MELD score (range) 1 day after SIRT: 8 (6–11) Median MELD score (range) 60 days after SIRT: 8 (6–14) There were 16 reportable AEs in the nine patients, but no grade 3/4 AEs. Most common AEs were nausea ($n = 3$), fatigue ($n = 3$), vomiting ($n = 3$), abdominal pain ($n = 2$) and ascites ($n = 2$) **Time on treatment/number of treatments:** Not reported	

ALT, alanine aminotransferase; AST, aspartate aminotransferase; IQR, interquartile range; QoL, quality of life; SE, standard error; TOF-PET, Time-of-Flight Positron emission tomography.

Appendix 7 Lower-priority studies not included in the systematic review of clinical effectiveness or considered for the network meta-analyses ($n = 28$)

Study (first author and year)	Intervention	Comparator	Reason for not including in the systematic review
Moroz 2001[53]	SIR-Spheres plus hepatic arterial chemotherapy	Hepatic arterial chemotherapy	Clinical advice that hepatic arterial chemotherapy is not applicable to current UK practice
Pellerito 2013[55]	SIR-Spheres	131-iodine Lipiodol	Clinical advice that 131-iodine Lipiodol is not applicable to current UK practice
Steel 2004[52]	TheraSphere	Hepatic arterial infusion of cisplatin	Clinical advice that hepatic arterial infusion of cisplatin is not applicable to current UK practice
Maccauro 2016[54]	Standard-dose TheraSphere	Personalised treatment planning TheraSphere	Clinical advice that standard-dose TheraSphere is not applicable to current UK practice
She 2014[159]	SIR-Spheres	TACE	Group imbalances make comparison meaningless (patients were allocated to SIRT if they were not eligible for TACE, e.g. had previously failed on TACE)
Kooby 2010[160]	SIR-Spheres	TACE	Study included a more advanced population than in other studies in the NMA of patients eligible for CTTs and there was a baseline imbalance between groups in relation to PVI
Kwok 2014[161]	SIR-Spheres	No SIR-Spheres	All patients included in the study opted for SIRT, but 16 were ineligible (primarily owing to lung shunt); the study compares those who received it with those who did not
Song 2017[162]	SIR-Spheres	Concurrent chemoradiation therapy	Clinical advice that concurrent chemoradiation therapy is not applicable to current UK practice
Oladeru 2016[163]	SIR-Spheres	External beam radiotherapy	Clinical advice that external beam radiotherapy is not applicable to current UK practice
Rühl 2009[164]	SIR-Spheres	High-dose-rate brachytherapy	Clinical advice that high-dose-rate brachytherapy is not applicable to current UK practice
D'Avola 2009[165]	SIR-Spheres	No SIRT (combination of conventional or experimental therapies or no therapy)	Comparator was a combination of conventional or experimental therapies or no therapy; conventional therapy patients were not reported separately; therefore, the trial was not informative for the NMA
Carr 2010[166]	TheraSphere	TACE	All patients had ECOG performance status of > 2 and therefore were a more advanced population than in other studies in the NMA of patients eligible for CTTs
Kallini 2018[167]	TheraSphere	TACE	No OS or PFS outcomes reported and therefore not informative for the NMA
Gabr 2017[168]	TheraSphere	TACE	Population of patients who had received a transplant; therefore, not comparable population with other studies in the NMA of patients eligible for CTTs

Study (first author and year)	Intervention	Comparator	Reason for not including in the systematic review
Riaz 2009[169]	TheraSphere	TACE	Group imbalances make comparison meaningless
Biederman 2018[170]	TheraSphere	TACE	Patients within Milan criteria, therefore not comparable population to other studies in the NMA of patients eligible for CTTs
Lewandowski 2009[118]	TheraSphere	TACE	No HRs or KM curves presented, therefore not informative for the NMA. In addition, patients received SIRT or TACE for downstaging; therefore, not comparable population to other studies in the NMA of patients eligible for CTTs
Ahmad 2005[171]	TheraSphere	TACE	No OS or PFS outcomes reported; therefore, not informative for the NMA
Padia 2017[172,173]	TheraSphere	TACE or DEB-TACE	Mixed population of BCLC A, B and C (70% within Milan criteria); therefore, not informative for the NMA of patients eligible for CTTs
Newell 2015[174]	TheraSphere	TACE or DEB-TACE	Mixed population of BCLC B and C patients; therefore, not informative for the NMA of patients eligible for CTTs
Taussig 2017[175]	TheraSphere	TACE or DEB-TACE	No OS or PFS outcomes reported; therefore, not informative for the NMA
McDevitt 2017[176]	TheraSphere	DEB-TACE	Mixed population of BCLC B and C patients, therefore not informative for the NMA of patients eligible for CTTs. Patients without main PVI could receive DEB-TACE; those with PVI received SIRT and therefore group imbalances
Akinwande 2015[177,178]	TheraSphere	DEB-TACE	Unclear population, but all patients had PVT; therefore, not informative for the NMA of patients eligible for CTTs
Biederman 2017[179,180]	TheraSphere	TACE combined with microwave ablation	Clinical advice that TACE combined with microwave ablation is not widely practised in the UK
Padia 2015[181]	TheraSphere	Ablation, chemoembolisation or BSC	Comparator was a combination of ablation, chemoembolisation and BSC. Chemoembolisation patients were not reported separately; therefore, the trial was not informative for the NMA of patients eligible for CTTs
Radunz 2017[182]	TheraSphere	TACE, radiofrequency ablation or no bridging therapy	Patients were eligible for transplant and received SIRT or TACE for bridging; therefore, not comparable population to other studies in the NMA of patients eligible for CTTs
Salem 2018[108]	TheraSphere	N/A	Non-comparative study
Ali 2018[183]	TheraSphere	N/A	Non-comparative study

N/A, not applicable.

Appendix 8 Risk-of-bias assessment results for retrospective comparative studies used in the network meta-analysis

Study (first author and year)	Inclusion criteria clearly defined	Representative sample from relevant population	Groups similar at baseline	Clearly described and consistently delivered intervention	Clearly described and consistently delivered comparator	Outcome assessors blinded	Missing outcome data balanced across groups	Free from suggestion of selective reporting	Overall judgement of risk of bias
Biederman 2015[38]	No	Unclear	Unclear	No	No	Unclear	Unclear	Unclear	High
Biederman 2016[39]	Yes	Yes	No	Yes	Yes	Unclear	Unclear	Unclear	High
Van Der Gucht 2017[40]	Yes	Yes	No	Yes	Yes	Unclear	Yes	Yes	High
Bhangoo 2015[41]	Yes	Yes	Unclear	Yes	Yes	Unclear	Unclear	Yes	Unclear
d'Abadie 2018[42]	No	Unclear	No	No	No	Unclear	Unclear	Yes	High
Gramenzi 2015[45]	Yes	Yes	No	Yes	Yes	Unclear	Unclear	Yes	High
de la Torre 2016[44]	Yes	Yes	No	Yes	Yes	Unclear	Unclear	Yes	High
Cho 2016[43]	Yes	Yes	No	Yes	Yes	Unclear	Yes	Yes	High

Appendix 9 Risk-of-bias assessment results for randomised controlled trials of comparative therapies used in the network meta-analysis

Trial (first author and year)	Risk of bias arising from the randomisation process	Risk of bias owing to deviation from the intended interventions	Missing outcome data (primary outcomes)	Risk of bias in measurement of the outcomes	Risk of bias in selection of the reported result	Overall judgement of risk of bias
Yu 2014[65]	Some concerns	Low	Low	Low	Low	Some concerns
Chang 1994[63]	Some concerns	Some concerns	Low	Low	Low	Some concerns
Meyer 2013[64]	Some concerns	Low	Low	Low	Low	Some concerns
Malagari 2010[66]	Some concerns	Some concerns	Low	Low	Low	Some concerns
Sacco 2011[59]	High	Low	Low	Low	Low	High

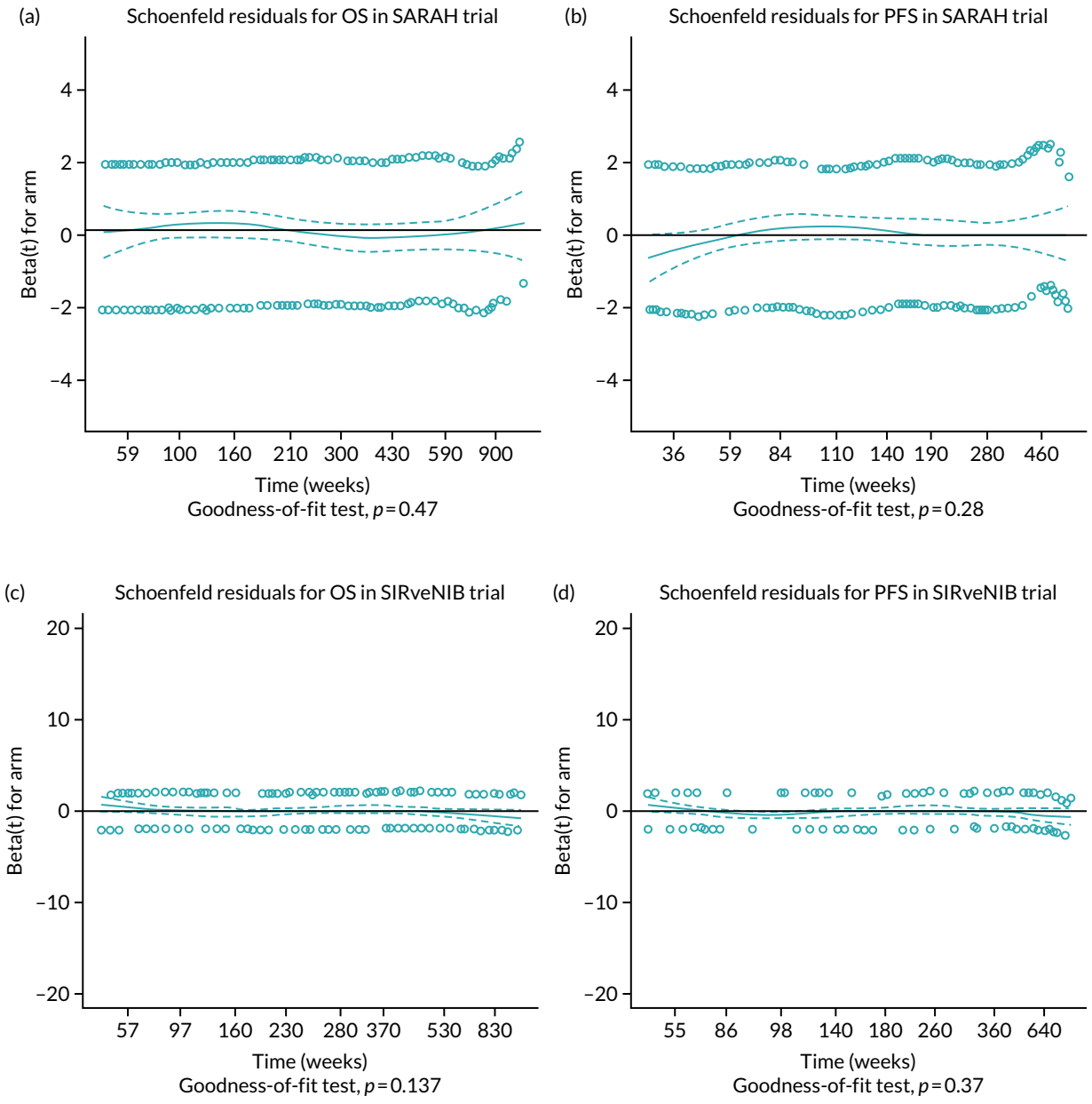
Appendix 10 Study details and results for studies of comparators included in the network meta-analysis

Study (first author, year and location)	Study design and funding source	Population	Intervention	Comparator	Main results
Yu 2014[65] China	Parallel-group RCT Funding: not reported	Patients with unresectable HCC with Child–Pugh class A or B and ECOG performance status of < 2	TAE ($n = 45$)	TACE ($n = 45$)	**OS:** TAE: median 24.3 months (95% CI 12.8 to 32.7 months) TACE: median 20.1 months (95% CI 9.3 to 31.2 months) **PFS:** TAE: median 6.5 months (95% CI 7.8 to 9.2 months) TACE: median 4.4 months (95% CI 1.6 to 7.2 months) **TTP:** TAE: median 8.4 months (95% CI 5.3 to 11.4 months) TACE: median 4.4 months (95% CI 1.7 to 7.1 months)
Malagari 2010[66] Greece	RCT Funding: not reported	Patients with HCC unsuitable for curative therapy and at high risk for surgery	DEB-TACE ($n = 48$)	TAE ($n = 47$)	**OS:** DEB-TACE: 100% were alive at 6 months and 85.3% at 12 months TAE: 100% were alive at 6 months and 86% at 12 months **PFS**: Not reported **TTP:** DEB-TACE: 42.4 ± 9.5 weeks TAE: 36.2 ± 9.0 weeks

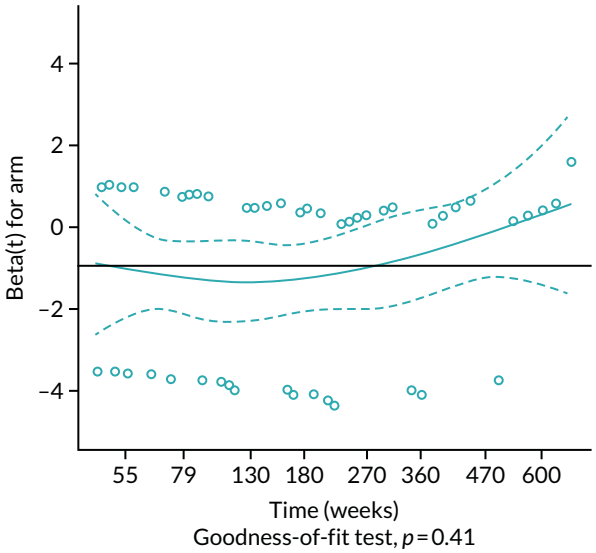
Study (first author, year and location)	Study design and funding source	Population	Intervention	Comparator	Main results
Sacco 2011[59] Italy	Single-centre RCT Funding: not reported	Patients with unresectable HCC with Child–Pugh class A or B, ECOG performance status of 0–1 and unsuitable for ablative treatments	TACE ($n = 34$)	DEB-TACE ($n = 33$)	**OS:** TACE: 83.6% were alive at 24 months DEB-TACE: 86.8% were alive at 24 months **PFS:** TACE: 80.1% were disease progression free DEB-TACE: 82.5% were disease progression free **TTP:** TACE: mean 24.2 months DEB-TACE: mean 15.6 months
Meyer 2013[64] UK	Phase II/III RCT Funding: National Institute for Health Research, Experimental Cancer Medicine Centre Network	Patients with unresectable HCC with Child–Pugh class A or B and ECOG performance status of 0–2	TAE ($n = 42$)	TACE ($n = 44$)	**OS:** HR 0.91, 95% CI 0.51 to 1.62 TAE: median 17.3 months TACE: median 16.3 months **PFS:** HR 0.87, 95% CI 0.52 to 1.45 TAE: median 7.2 months TACE: median 7.5 months **TTP:** Not reported
Chang 1994[63] China	Single-centre RCT Funding: not reported	Patients with inoperable HCC and Child–Pugh class A or B	TACE ($n = 22$)	TAE ($n = 24$)	**OS:** TACE: 52.5% were alive at 1 year and 26.2% were alive at 2 years TAE: 72.5% were alive at 1 year and 39.5% were alive at 2 years **PFS:** Not reported **TTP:** Not reported

Appendix 11 Schoenfield residual plots for the studies included in the network meta-analysis for adults with unresectable hepatocellular carcinoma who are ineligible for conventional transarterial therapy

Studies: (a) and (b) SARAH;[19] (c) and (d) SIRveNIB;[21] (e) Biederman *et al.*;[39] (f) and (g) Van Der Gucht *et al.*[40]

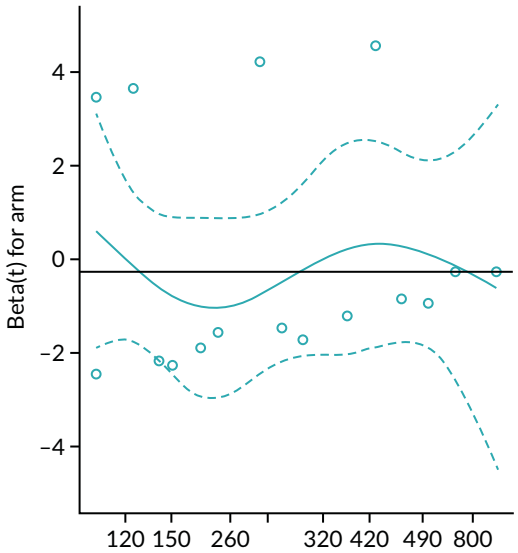


(e) Schoenfeld residuals for OS in Biederman *et al.*



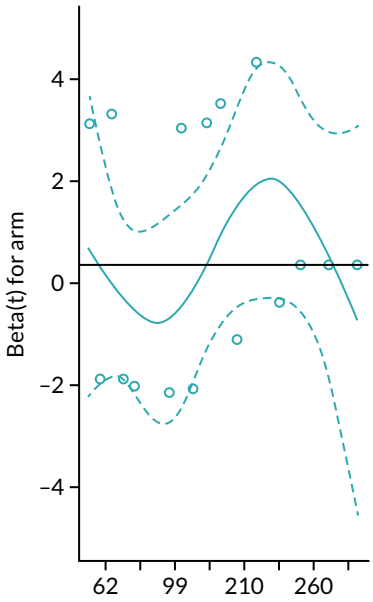
Goodness-of-fit test, $p = 0.41$

(f) Schoenfeld residuals for OS in Van Der Gucht *et al.*



Goodness-of-fit test, $p = 0.99$

(g) Schoenfeld residuals for PFS in Van Der Gucht *et al.*



Goodness-of-fit test, $p = 0.49$

Appendix 12 Results of the network meta-analysis for all patients in the intention-to-treat population

There were three studies included in the NMA of all adults with unresectable HCC who are ineligible for CTT: SARAH,[19] SIRveNIB[21] and Kudo.[184] There were no significant differences in OS between the treatments when all patients, not just Child–Pugh A patients, were included (see *Table 39*). SIR-Spheres showed a non-significant improvement in PFS when compared with sorafenib (HR 0.97, 95% CrI 0.84 to 1.12) but showed a significant reduction in PFS compared with lenvatinib (HR 1.34, 95% CrI 1.01 to 1.73). The HR estimates for each treatment comparison are presented in *Tables 41* and *42*.

TABLE 39 Overall survival and PFS results for all adults with unresectable HCC who are ineligible for CTT in the ITT population

		HR (95% CrI)	
Intervention	**Comparator**	**OS**	**PFS**
SIR-Spheres	Sorafenib	1.14 (0.98 to 1.32)	0.97 (0.84 to 1.12)
SIR-Spheres	Lenvatinib	1.10 (0.78 to 1.49)	1.34 (1.01 to 1.73)
Lenvatinib	Sorafenib	1.06 (0.79 to 1.40)	0.73 (0.58 to 0.91)
DIC		−3.22	−4.86
pD		2.00	2.00

pD, number of parameters.

Scenario 2: inclusion of Biederman *et al.* and Van Der Gucht *et al.* into network meta-analysis for all adults in the intention-to-treat population

The two retrospective comparative studies, Biederman *et al.*[39] and Van Der Gucht *et al.*,[40] were added to the NMA of all patients with unresectable HCC, who are ineligible for CTT, which allowed a comparison to be made with TheraSphere. A subgroup of 42 patients with advanced-stage HCC was used from the Van Der Gucht *et al.*[40] study. The fixed-effects model was chosen as the DIC and the number of parameters were lower. There was a significant improvement in OS with TheraSphere when compared with sorafenib (HR 0.53, 95% CrI 0.31 to 0.84), SIR-Spheres (HR 0.46, 95% CrI 0.28 to 0.72) and lenvatinib (HR 0.51, 95% CrI 0.28 to 0.86). As discussed earlier, Biederman *et al.*[39] and Van Der Gucht *et al.*[40] both have large treatment effects and, therefore, result in TheraSphere being significantly better for OS in the NMA. There were no notable differences between any of the other treatments for OS (see *Table 40*).

TABLE 40 Network meta-analysis results of all adults with unresectable HCC who are ineligible for CTT including the studies by Biederman *et al.*[39] and Van Der Gucht *et al.*[40]

Intervention	Comparator	OS HR (95% CrI), fixed effects
SIR-Spheres	Sorafenib	1.14 (1.01 to 1.28)
SIR-Spheres	Lenvatinib	1.10 (0.80 to 1.48)
TheraSphere	SIR-Spheres	0.46 (0.28 to 0.72)
TheraSphere	Sorafenib	0.53 (0.31 to 0.84)
TheraSphere	Lenvatinib	0.51 (0.28 to 0.86)
Lenvatinib	Sorafenib	1.06 (0.79 to 1.40)

TABLE 41 Hazard ratio estimates (95% CrI) for OS for each treatment comparison for all patients in the NMA ITT population

Sorafenib	0.88 (0.78 to 0.99)	0.96 (0.71 to 1.27)
1.14 (1.01 to 1.28)	SIR-Spheres	1.1 (0.80 to 1.48)
1.06 (0.79 to 1.40)	0.93 (0.67 to 1.25)	Lenvatinib

Significant differences in the relative effects between a pair of agents are given in bold.

TABLE 42 Hazard ratio estimates (95% CrI) for PFS for each treatment comparison for all patients in the NMA ITT population

Sorafenib	1.04 (0.89 to 1.20)	1.61 (0.45 to 4.15)
0.97 (0.84 to 1.12)	SIR-Spheres	1.56 (0.43 to 4.07)
0.86 (0.24 to 2.22)	0.89 (0.25 to 2.31)	Lenvatinib

Appendix 13 Random-effects network meta-analysis results

TABLE 43 Random-effects NMA OS results of base-case NMA, including Biederman *et al.*[39] in the ITT and per-protocol populations: adults with unresectable HCC who are ineligible for CTT

		HR (95% CrI)	
Intervention	**Comparator**	**ITT**	**Per protocol**
SIR-Spheres	Sorafenib	0.94 (0.68 to 1.26)	1.13 (0.86 to 1.46)
SIR-Spheres	Lenvatinib	0.92 (0.52 to 1.51)	1.11 (0.66 to 1.74)
TheraSphere	SIR-Spheres	0.46 (0.19 to 0.94)	0.42 (0.19 to 0.82)
TheraSphere	Sorafenib	0.42 (0.18 to 0.83)	0.48 (0.20 to 0.97)
TheraSphere	Lenvatinib	0.41 (0.15 to 0.89)	0.46 (0.17 to 1.02)
Lenvatinib	Sorafenib	1.07 (0.67 to 1.63)	1.07 (0.70 to 1.58)
SD		0.11 (0.004 to 0.352)	0.13 (0.005 to 0.378)
DIC		0.9	2.1
pD		3.4	3.4

pD, number of parameters.

TABLE 44 Random-effects OS and PFS outcomes for all patients in the NMA ITT population: adults with unresectable HCC who are ineligible for CTT

		HR (95% CrI), random effects	
Intervention	**Comparator**	**OS**	**PFS**
SIR-Spheres	Sorafenib	0.97 (0.73 to 1.26)	1.15 (0.89 to 1.45)
SIR-Spheres	Lenvatinib	1.58 (0.40 to 4.21)	1.12 (0.68 to 1.73)
Lenvatinib	Sorafenib	0.87 (0.23 to 2.33)	1.07 (0.70 to 1.57)
SD		0.11 (0.004 to 0.352)	0.12 (0.005 to 0.367)
DIC		−1.69	2.18
pD		2.4	2.5

pD, number of parameters.

TABLE 45 Random-effects NMA of all adults with unresectable HCC who are ineligible for CTT, including studies Biederman *et al.*[39] and Van Der Gucht *et al.*[40]

Intervention	Comparator	OS HR (95% CrI)
SIR-Spheres	Sorafenib	1.15 (0.89 to 1.45)
SIR-Spheres	Lenvatinib	1.11 (0.68 to 1.73)
TheraSphere	SIR-Spheres	0.50 (0.26 to 0.89)
TheraSphere	Sorafenib	0.58 (0.29 to 1.06)
TheraSphere	Lenvatinib	0.56 (0.24 to 1.13)
Lenvatinib	Sorafenib	1.07 (0.70 to 1.57)

TABLE 46 Results of random-effects base-case NMA, excluding the SIRveNIB study

		OS HR (95% CrI)	
Intervention	Comparator	ITT population	Per-protocol population
SIR-Spheres	Sorafenib	1.16 (0.71 to 1.78)	1.03 (0.63 to 1.61)
SIR-Spheres	Lenvatinib	1.13 (0.55 to 2.09)	1.02 (0.49 to 1.88)
Lenvatinib	Sorafenib	1.08 (0.65 to 1.71)	1.08 (0.65 to 1.71)
SD		0.15 (0.006 to 0.426)	0.15 (0.006 to 0.426)
DIC		0.92	1.1
pD		2.0	2.0

pD, number of parameters.

Appendix 14 Quality assessment of identified economic evidence

TABLE 47 Quality assessment of economic studies: modified Philips checklist[88]

Assessment criteria	Study	
	Rostambeigi *et al.*[91,92]	Rognoni *et al.*[89,90]
Structure		
1. Is there a clear statement of the decision problem?	Yes	Yes
2. Is the perspective and scope of the model stated clearly?	No	Yes
3. Are the model inputs consistent with the stated perspective?	N/A	Yes
4. Are the outcomes of the model consistent with the perspective, scope and overall objective of the model?	N/A	Yes
5. Are the structural assumptions reasonable given the overall objective, perspective and scope of the model?	No	Yes
6. Is there a clear definition and justification for the alternative options under evaluation?	Yes	Yes
7. Is the chosen model type appropriate given the decision problem and specified causal relationships within the model?	No	Yes
8. Are the time horizon of the model, the duration of treatment and the duration of treatment effect described and appropriately justified?	No	Yes
9. Do the disease states (state transition model) or the pathways (decision tree model) reflect the underlying biological process of the disease in question and the impact of interventions?	No	Yes
10. Is the cycle length defined and justified in terms of the natural history of disease?	No	Yes
Data		
11. Are the data identification methods transparent and appropriate given the objectives of the model?	Yes	Yes
12. Has the quality of the data been assessed appropriately?	No	N/A
13. Is the data modelling methodology based on justifiable statistical and epidemiological techniques?	Partial	Yes
14. Is the choice of baseline data described and justified?	N/A	Yes
15. Are transition probabilities calculated appropriately?	N/A	Yes
16. Has a half-cycle correction been applied to both costs and outcomes?	N/A	No
17. If relative treatment effects have been derived from trial data, have they been synthesised using appropriate techniques?	No	N/A
18. Have the methods and assumptions used to extrapolate short-term results to final outcomes been documented and justified?	Partial	Partial
19. Have alternative assumptions been explored through sensitivity analysis?	Partial	Yes
20. Have assumptions regarding the continuing effect of treatment once treatment is complete been documented and justified?	No	N/A

continued

TABLE 47 Quality assessment of economic studies: modified Philips checklist[88] (*continued*)

Assessment criteria	Study	
	Rostambeigi *et al.*[91,92]	Rognoni *et al.*[89,90]
Costs and discounting		
21. Are the costs incorporated into the model described and justified?	Yes	Yes
22. Has the source for all costs been described?	Yes	Yes
23. Have discount rates been described and justified given the target decision-maker?	N/A	Yes
24. Were currency, price date and price adjustments/currency conversion information stated?	No	Yes
HRQoL		
25. Are the utilities incorporated into the model appropriate?	N/A	Yes
26. Is the source for the utility weights referenced?	N/A	Yes
Validation		
27. Has heterogeneity been dealt with by running the model separately for different subgroups?	Yes	N/A
28. Have the results of the model been compared with those of previous models and any differences in results explained?	No	Partial

N/A, not applicable.

Appendix 15 Model parameters from submitted economic models

Sirtex model parameters: conventional transarterial therapy-eligible model

TABLE 48 Summary of TACE treatment costs: Sirtex CTT-eligible model

Input	Inflated value	Source
Scenario 1: CTT cost from literature		
Proportion of CTT with DEB-TACE	25%	Fateen *et al.*[105]
TACE cost	£9801.00	Fateen *et al.*[105]
DEB-TACE cost	£5727.03	Fateen *et al.*[105]
CTT cost (literature)	£8792.59	Calculated
***Scenario 2: CTT resource use from literature, with* National Schedule of Reference Costs 2017–2018[107]**		
Drug-eluding beads	£594.30	Fateen *et al.*[105]
TACE length of stay (days)	2.37	Fateen *et al.*[105]
DEB-TACE length of stay (days)	2.81	Fateen *et al.*[105]
Mean number of TACE procedures	3.03	Fateen *et al.*[105]
Mean number of DEB-TACE procedures	1.43	Fateen *et al.*[105]
Proportion of CTT with DEB-TACE	25%	Fateen *et al.*[105]
TACE cost	£12,620.41	Calculated
DEB-TACE cost	£7911.80	Calculated
CTT cost (reference costs)	£11,454.91	Calculated
***Scenario 3: CTT resource use from survey, literature with* National Schedule of Reference Costs 2017–2018[107]**		
Drug-eluding beads	£594.30	Fateen *et al.*[105]
TACE length of stay (days)	2.37	Fateen *et al.*[105]
DEB-TACE length of stay (days)	2.81	Fateen *et al.*[105]
Mean number of TACE procedures	2.5	Sirtex resource use survey (personal communication)
Mean number of DEB-TACE procedures	2.83	Sirtex resource use survey (personal communication)
Proportion of CTT with DEB-TACE	63%	Sirtex resource use survey (personal communication)
TACE cost	£10,412.88	Calculated
DEB-TACE cost	£15,676.06	Calculated
CTT cost	£13,702.37	Calculated

Adapted with permission from Sirtex Medical Ltd.[102]

TABLE 49 Summary of cost of SIRT: Sirtex CTT-eligible model

	SIR-Spheres		TheraSphere	
Parameter	**Value**	**Source**	**Value**	**Source**
Outpatient costs for code YR57Z	£1123.15	*National Schedule of Reference Costs 2017–2018*[107]	£1123.15	*National Schedule of Reference Costs 2017–2018*[107]
Inpatient cost/day for YR57Z	£1757.45		£1757.45	
SIRT	£8000.00	Sirtex[102]	£8000.00	Sirtex[102]
Survey results				
Number of work-ups	1.05	Survey	1.05	Assumed same as SIR-Spheres
Length of stay for work-up (days)	0.69		0.69	
Number of procedures	1.20		1.20	
Length of stay for procedure (days)	1.19		1.19	
Cost of work-up	£1175.56	–	£1175.56	–
Cost of procedure	£2500.13	–	£2500.13	–
Total cost	£13,239.33	–	£13,239.33	–
Survey results with outpatient procedures				
Number of work-ups	1.05	Survey	1.05	Assumed same as SIR-Spheres
Length of stay for work-up (days)	Outpatient		Outpatient	
Number of procedures	1.20		1.20	
Length of stay for procedure (days)	Outpatient		Outpatient	
Cost of work-up	£1175.56	–	£1175.56	–
Cost of procedure	£1342.67	–	£1342.67	–
Total cost	£12,081.87	–	£12,081.87	–
The Christie NHS Foundation Trust results				
Number of work-ups	Confidential information has been removed	The Christie NHS Foundation Trust data (personal communication)	Confidential information has been removed	The Christie NHS Foundation Trust data (personal communication)
Length of stay for work-up (days)	Confidential information has been removed		Confidential information has been removed	
Number of procedures	Confidential information has been removed		Confidential information has been removed	
Length of stay for procedure (days)	Confidential information has been removed		Confidential information has been removed	
Cost of work-up	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed
Cost of procedure	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed
Total cost	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed

TABLE 49 Summary of cost of SIRT: Sirtex CTT-eligible model (*continued*)

Parameter	SIR-Spheres		TheraSphere	
	Value	Source	Value	Source
Sangro* et al.[69] *and Salem* et al.[108] *for number of procedures, rest survey				
Number of work-ups	1.05	Survey	1.05	Survey
Length of stay for work-up (days)	0.69	Survey	0.69	Survey
Number of procedures	1.08	ENRY reigster[69]	1.58	PREMIERE[108]
Length of stay for procedure (days)	1.19	Survey	1.19	Survey
Cost of work-up	£1175.56	–	£1175.56	–
Cost of procedure	£2252.24	–	£3298.08	–
Total cost	£12,043.19	–	£17,089.64	–

Adapted with permission from Sirtex Medical Ltd.[102]

TABLE 50 Adverse event rates: Sirtex CTT-eligible model

AE	TACE ($n = 19$)	TheraSphere ($n = 24$)	Unit costs	Source for unit cost
Abdominal pain	0%	4%	£42.19	NICE TA474[11] sorafenib technology appraisal
Elevated aspartate aminotransferase level	11%	0%	£634.50	NICE TA551[12] lenvatinib technology appraisal
Hypoalbuminemia	0%	4%	£634.50	Assumed average of elevated aspartate aminotransferase and blood bilirubin
Increased blood bilirubin	5%	8%	£916.47	NICE TA551[12] lenvatinib technology appraisal
Leukopenia	0%	4%	£215.00	NICE TA509 pertuzumab[185]
Neutropenia	11%	0%	£2097.50	*National Schedule of Reference Costs 2017–2018*[107] (WJ11Z)
Total costs	£346.34	£108.99		

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Sirtex model parameters: conventional transarterial therapy-ineligible model

TABLE 51 Summary of the base-case utility values: Sirtex CTT-ineligible model

Comparator	Utility value: mean (standard error)	Reference
Pre progression: SIR-Spheres	0.762 (0.078)	Post hoc analyses of the SARAH trial[19] for the low tumour burden/ALBI 1 subgroup
Pre progression: sorafenib	0.746 (0.076)	
Post progression: SIR-Spheres	0.738 (0.075)	
Post progression: sorafenib	0.722 (0.074)	
After subsequent treatment with curative intent	0.762 (0.078)	Assumed same as the pre-progression utilities with SIR-Spheres

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TABLE 52 Assumptions and costs of the SIRT procedure: Sirtex CTT-ineligible model

Cost item	Value	Source
Outpatient costs for code YR57Z	£1123.15	*National Schedule of Reference Costs 2017–2018*[107]
Inpatient cost/day for YR57Z	£1757.45	
SIR-Spheres	£8000.00	Sirtex[102]
Number of work-ups per patient	1.05	Resource use survey
Length of stay for work-up (days)	0.69	
Number of treatments per patient	1.20	
Length of stay for treatment (days)	1.19	
Cost of a single work-up	£1175.56	Subtotal
Cost of a single treatment	£2500.13	Subtotal
Total cost	£13,239.33	–

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TABLE 53 Proportions of treatments with curative intent observed in the SARAH trial: Sirtex CTT-ineligible model

Proportions	After SIRT	After sorafenib
% of liver resection among treatments with curative intent	33.3	0.0
% of liver transplantation among treatments with curative intent	16.7	33.3
% of ablation among treatments with curative intent	58.3	66.7

Reproduced with permission from Sirtex Medical Ltd.[102]

TABLE 54 Health state costs: Sirtex CTT-ineligible model

Cost item	Pre-progression post SIRT (per month)	Pre-progression on sorafenib/lenvatinib (per month)	At progression (one off)	Progressive disease (per month)
Medical staff contact	£102.84	£126.49	£118.50	£222.96
Diagnostic procedures	£130.26	£134.58	£89.28	£6.15
Inpatient care	£6.80	£20.29	–	£78.50
PSS	£5.83	£5.83	–	£191.76
Total	£245.74	£287.19	£207.79	£499.37

Reproduced with permission from Sirtex Medical Ltd.[102]

TABLE 55 Adverse event costs: Sirtex CTT-ineligible model

AE	Inflated cost	Reported costs	Costing year	Source
Abdominal pain	£42.19	£40.15	2014/15	NICE TA474[11] sorafenib TA
Alopecia	£18.59	£17.69	2014/15	NICE TA474[11] sorafenib TA
Anaemia	£1319.84	£1283.67	2015/16	NICE TA514[13] regorafenib TA
Anorexia	£657.86	£639.83	2016/17	NICE TA535[154] lenvatinib and sorafenib
Ascites	£1713.98	£1667.00	2015/16	NICE TA514[13] regorafenib TA
Aspartate aminotransferase level increased	£634.50	£617.11	2016/17	NICE TA551[124] lenvatinib TA
Asthenia	£677.68	£659.11	2016/17	NICE TA551[124] lenvatinib TA
Blood bilirubin level increased	£916.47	£891.35	2016/17	NICE TA551[124] lenvatinib TA
Cardiac failure, congestive	£1979.71	£1979.71	2017/18	*National Schedule of Reference Costs 2017–2018*:[107] weighted-average HRG codes EB03A and EB03E
Diarrhoea	£605.13	£588.54	2016/17	NICE TA551[124] lenvatinib TA
Fatigue	£677.68	£659.11	2016/17	NICE TA551[124] lenvatinib TA
Gamma-glutamyl transferase level increased	£634.50	£617.11	2016/17	NICE TA551[124] lenvatinib TA
Haematological biological abnormalities	£1319.84	£1283.67	2015/16	NICE TA514[13] regorafenib TA
Haemorrhage	£0.00	£0.00	2014/15	NICE TA474[11] sorafenib TA
Hand–foot skin reaction	£897.98	£873.37	2015/16	NICE TA514[13] regorafenib TA
Hypertension	£888.12	£863.78	2016/17	NICE TA551[124] lenvatinib TA
Hypophosphataemia	£1297.52	£1261.96	2015/16	NICE TA514[13] regorafenib TA
Liver dysfunction	£1713.98	£1667.00	2015/16	NICE TA514[13] regorafenib TA
Nausea/vomiting	£82.18	£78.20	2014/15	NICE TA474[11] sorafenib TA
Other increase in liver function	£634.50	N/A	N/A	NICE TA551[124] lenvatinib TA
Palmar–plantar erythrodysesthesia syndrome	£443.80	£431.64	2016/17	NICE TA551[124] lenvatinib TA
Platelet count decreased	£634.50	£617.11	2016/17	NICE TA551[124] lenvatinib TA
Proteinuria	£812.04	£789.78	2016/17	NICE TA551[124] lenvatinib TA
Rash/desquamation	£71.09	£67.65	2014/15	NICE TA474[11] sorafenib TA
Weight decreased	£665.35	£647.11	2016/17	NICE TA551[124] lenvatinib TA

N/A, not applicable; TA, technology appraisal.
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BTG model parameters: conventional transarterial therapy-eligible model

TABLE 56 Summary of per-cycle transition probabilities: BTG CTT-eligible model

Parameter	Per-cycle transition probability	Source
'Watch and wait' to pre transplant	SIRT = 10.8% CTT = 5.8%	Lewandowski *et al.*[118]
'Watch and wait' to pharmacological management	SIRT = 7.8% CTT = 12.8%	Calculation
'Watch and wait' to 'watch and wait'	81.4%	Lewandowski *et al.*[118]
Pre transplant to pharmacological management	2.2%	National Audit for Liver Transplant (personal communication)
Pre transplant to post transplant	13.9%	NHS Annual Report on Liver Transplantation 2017/18[120]
Pre transplant to pre transplant	84.0%	Calculation

TABLE 57 Summary of per-cycle mortality parameters: BTG CTT-eligible model

Health state	Mortality rate (per cycle)	Source
Watch and wait	3.88%	Assumed the same as pre transplant
Pre transplant	3.88%	NHS England. Schedule 2 – The Services. A. Service Specifications. 170003/S. Liver Transplantation service (Adults)[186]
Pharmacological management	7.74%	Derived from the median OS for BSC from the NICE sorafenib submission (TA474[11])
Post transplant 1	1.39%	Bellavance *et al.*[122]
Post transplant 2	1.39%	Bellavance *et al.*[122]
Post transplant 3	1.39%	Bellavance *et al.*[122]
No HCC (post transplant)	0.29%	NHS Survival rates following transplantation[187]

Note that one cycle is equal to 4 weeks.
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TABLE 58 Adverse event rates: BTG CTT-eligible model

AE	Rate (%)					
	TheraSphere	SIR-Spheres	Quirem Spheres	TACE	DEB-TACE	TAE
Aspartate aminotransferase level increase	0.0	0.0	0.0	0.0	0.0	0.0
Proteinuria	0.0	0.0	0.0	0.0	0.0	0.0
Blood bilirubin level increase	0.0	0.0	0.0	0.0	0.0	16.0
Diarrhoea	0.0	0.0	0.0	0.0	0.0	0.0
Fatigue	1.9	2.3	2.3	0.0	0.0	8.0
Gamma-glutamyl transferase level increase	0.0	0.0	0.0	0.0	0.0	26.0
Hypertension	0.0	0.0	0.0	0.0	0.0	0.0
Weight decrease	0.0	0.0	0.0	0.0	0.0	0.0
Platelet count decrease	0.0	0.0	0.0	0.0	0.0	0.0
Palmar–plantar erythrodysesthesia syndrome	0.0	0.0	0.0	0.0	0.0	0.0
Ascites	6.1	2.3	2.3	0.0	0.0	0.0
Cholecystitis	1.9	5.0	5.0	0.0	1.1	0.0
Hepatic encephalopathy	2.8	8.0	8.0	0.0	0.0	0.0
Post-procedural pain	1.9	1.2	1.2	18.2	0.0	21.0

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TABLE 59 Utility values: BTG CTT-eligible model

Health state	Source utility	Applied utility[a]	Source
Watch and wait	0.75	0.534	TA535[154] (pre progression)
Pre transplant	0.75	0.534	TA535[154] (pre progression)
Post transplant 1	0.69	0.474	Lim *et al.*[125]
Post transplant 2	0.69	0.473	Lim *et al.*[125]
Post transplant 3	0.69	0.473	Lim *et al.*[125]
No HCC post transplant	0.75	0.534	TA535[154] (pre progression)
Pharmacological management	0.72	0.499	TA535[154] (calculated as an average of pre-progression and post-progression utilities)

a Based on the age in the first cycle of the model.

TABLE 60 Micro-costing of SIRT work-up assessment procedure: BTG CTT-eligible model

Work-up factors: costs included in the BTG analysis	Cost
Band 6 technician: 30 minutes (unit cost per hour: £15.96)	£7.98
Band 7 clinical scientist: 30 minutes (unit cost per hour: £19.06)	£9.53
MAA body SPECT[a]	£353.00
Lung shunt calculation – band 7 clinical scientist: 10 minutes (unit cost per hour: £19.06)	£3.18
Volumetary – band 7 clinical scientist: 1 hour (unit cost per hour: £19.06)	£19.06
Volumetary band radiologist: 1 hour (unit cost per hour: £75.16)	£75.16
Total cost	£467.91
Additional costs provided by BTG following the company submission	
One radiologist: 2 hours (unit cost per hour: £75.16)	£150.30
Two band 6 nurses: 3 hours (unit cost per hour: £23.82)	£142.92
One band 6 radiographer: 3 hours (unit cost per hour: £23.82)	£71.46
One band 4 co-ordinator: 1 hour (unit cost per hour: £16.30)	£16.30
Blood work	£11.35
Total cost	£860.32

a There is not currently an NHS tariff for a MAA body SPECT. However, it is thought that a sum of the HRG codes (from the National Tariff Payment System) for the following is suitable for the total cost of a MAA body SPECT: a whole-body SPECT for one area [RN04A: £147 minus the agent cost (£26) = £121]; a whole-body SPECT for two areas [£180 minus the agent cost (£22) = £158]; MAA consumable agent (£74).[107]

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TABLE 61 Unit costs of AEs: BTG CTT-eligible model

Item	Unit cost	Source
Aspartate aminotransferase level increase	£615.76	*National Schedule of Reference Costs 2017–2018*.[107] Hospitalisation. Average non-elective short stay
Proteinuria	£657.76	*National Schedule of Reference Costs 2017–2018*.[107] Average non-elective short stay (for hospitalisation) at £615.76 Plus a nurse visit (GP practice): £42 (PSSRU 2018[106] – cost per hour including qualifications)
Blood bilirubin level increase	£886.56	*National Schedule of Reference Costs 2017–2018*.[107] Average non-elective short stay (for hospitalisation) at £615.76 Plus CT scan at £103.95. Weighted average of RD10Z–RD28Z. Adults only. *National Schedule of Reference Costs 2017–2018*[107] Plus £166.85: outpatient consultant-led, non-admitted face-to-face attendance, follow up (medical oncology). Code WF01A. *National Schedule of Reference Costs 2017–2018*[107]
Diarrhoea	£561.30	*National Schedule of Reference Costs 2017–2018*[107] – FD10K. Non-Malignant Gastrointestinal Tract Disorders without Interventions, with CC Score 6–10 – non-elective short stay
Fatigue	£657.76	*National Schedule of Reference Costs 2017–2018*.[107] Average non-elective short stay (for hospitalisation) at £615.76 Plus a nurse visit (GP practice) £42 (PSSRU 2018[106] – cost per hour including qualifications)

TABLE 61 Unit costs of AEs: BTG CTT-eligible model (*continued*)

Item	Unit cost	Source
Gamma-glutamyltransferase level increase	£615.76	*National Schedule of Reference Costs 2017–2018*.[107] Average non-elective short stay
Hypertension	£856.61	*National Schedule of Reference Costs 2017–2018*.[107] Average non-elective short stay (for hospitalisation) at £615.76 Plus 2 GP appointments (9.22 minutes) at £37 each (PSSRU 2018[106] – cost per hour including qualifications) Plus £166.85: outpatient consultant-led, non-admitted face-to-face attendance, follow up (medical oncology). Code WF01A. *National Schedule of Reference Costs 2017–2018*[107]
Weight decrease	£646.76	Hospitalisation: *National Schedule of Reference Costs 2017–2018*,[107] average cost of non-elective short stay (£615.76) Plus dietitian (PSSRU 2018[106]) – dietician band 4 cost per working hour (£31)
Platelet count decrease	£615.76	*National Schedule of Reference Costs 2017–2018*.[107] Hospitalisation. Average non-elective short stay
Palmar–plantar erythrodysesthesia syndrome	£413.03	*National Schedule of Reference Costs 2017–2018*[107] – JD07J Skin Disorders without Interventions, with CC score 2–5 – non-elective short stay
Ascites	£615.76	*National Schedule of Reference Costs 2017–2018*.[107] Hospitalisation. Average non-elective short stay
Cholecystitis	£507.81	Weighted average of GA07C-E. Intermediate, Hepatobiliary or Pancreatic Procedures, with CC Score 0–3 +
Hepatic encephalopathy	£615.76	*National Schedule of Reference Costs 2017–2018*.[107] Hospitalisation. Average non-elective short stay
Post-procedural pain	£615.76	*National Schedule of Reference Costs 2017–2018*.[107] Hospitalisation. Average non-elective short stay

Adapted with permission from BTG Ltd.[103]

TABLE 62 Summary of unit costs: BTG CTT-eligible model

Item	Unit cost	Source
Treatment and aftercare costs		
TheraSphere	£8000	Clinician informed
QuiremSpheres	£8000	Assumed the same as TheraSphere
SIR-Spheres	£8000	NICE Medtech Innovation Briefing[188]
Sorafenib	£3576.56	NICE BNF[115]
BSC	£0.00	Assumed
Doxorubicin (loaded on to DEB-TACE)	£109	Clinician informed
Drug-eluting beads (DEB-TACE)	£550	
Lipiodol (TACE)	£250	
Bland beads (TAE)	£40	
Ciclosporin immunosuppressants	£68.28	NICE BNF[115]

continued

TABLE 62 Summary of unit costs: BTG CTT-eligible model (*continued*)

Item	Unit cost	Source
Admissions and procedure costs		
Hospitalisation (general)	£1928	*National Schedule of Reference Costs 2017–2018*.[107] Weighted average of HRG GC12C–GC12K
Outpatient attendance	£167	*National Schedule of Reference Costs 2017–2018*.[107] Consultant-led: first attendance non-admitted face to face. Code 105 hepatobiliary and pancreatic surgery
Embolisation procedure	£2790	*National Schedule of Reference Costs 2017–2018*.[107] HRG code YR57Z
SIRT work-up	£467.91	The Christie NHS Foundation Trust (personal communication)
Liver transplant procedure	£17,340	*National Schedule of Reference Costs 2017–2018*.[107] HRG code GA15A
Liver resection procedure	£4994	*National Schedule of Reference Costs 2017–2018*.[107] Weighted average of HRG code GA06
Physician costs		
Oncologist	£166.85	*National Schedule of Reference Costs 2017–2018*.[107] Code WF01A. Non-Admitted Face-to-Face Attendance, Follow-up. Medical oncology
Hepatologist	£262.40	*National Schedule of Reference Costs 2017–2018*.[107] WF01A Consultant-led, Non-Admitted Face-to-Face Attendance, Follow-up (hepatology)
Macmillan nurse	£42	*PSSRU Unit Costs of Health and Social Care 2018*.[106] Nurse (GP practice). Cost per hour, including qualifications
Gastroenterologist	£146.29	*National Schedule of Reference Costs 2016/17*.[189] WF01A Consultant-led, Non-Admitted Face-to-Face Attendance, Follow-up (gastroenterology)
Radiologist	£152.27	*National Schedule of Reference Costs 2016/17*.[189] WF01A Consultant-led, Non-Admitted Face-to-Face Attendance, Follow-up (interventional radiology)
Clinical nurse specialist	£42	*PSSRU Unit Costs of Health and Social Care 2018*.[106] Nurse (GP practice). Cost per hour, including qualifications
Palliative care physician/care	£42	
GP	£37	*PSSRU Unit Costs of Health and Social Care 2018*.[106] Cost per 9.22-minute session, including qualifications
Laboratory tests		
Full blood count	£2.32	*National Schedule of Reference Costs 2017–2018*.[107] Weighted average of DAPS03, DAPS05 and DAPS08 (integrated blood services, haematology and phlebotomy)
Liver function tests	£20.07	*National Schedule of Reference Costs 2017–2018*.[107] Weighted average of DAPS01 and DAPS02
Alpha fetoprotein test	£20.07	
INR	£2.32	*National Schedule of Reference Costs 2017–2018*.[107] Weighted average of DAPS03, DAPS05 and DAPS08 (integrated blood services, haematology and phlebotomy)
Biochemistry	£1.11	*National Schedule of Reference Costs 2017–2018*.[107] DAPS04 (clinical biochemistry)
Endoscopy	£499.51	*National Schedule of Reference Costs 2017–2018*.[107] FE50A (Wireless Capsule Endoscopy, 19 years and over). Outpatient procedures
CT scan	£103.95	*National Schedule of Reference Costs 2017–2018*.[107] Weighted average of RD10Z–RD28Z Adults only
MRI scan	£145.56	*National Schedule of Reference Costs 2017–2018*.[107] Weighted average of all MRI currency codes (adult only, excluding cardiac magnetic resonance imaging) (RD01A, RD02A, RD03Z, RD04Z, RD05Z, RD06Z and RD07Z)
Ultrasound scan	£52.06	*National Schedule of Reference Costs 2017–2018*.[107] HRG codes RD40Z and RD41Z Ultrasound scan with duration < 20 mins, weighted average of cost with/without contrast

Adapted with permission from BTG Ltd.[103]

TABLE 63 Health state costs: BTG CTT-eligible model

Item	Cost per cycle
Total watch and wait	£539.16
Total pre transplant	£577.42
Total post transplant 0–1	£971.71
Total post transplant 1–2	£1049.22
Total post transplant 2–3	£516.42
No HCC post transplant	£502.49
Resection	£345.07
No HCC other	£306.50
Pharmacological management	£1308.57

Note that one cycle is equal to 4 weeks.
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BTG model parameters: conventional transarterial therapy-ineligible model

TABLE 64 Utility values: BTG CTT-ineligible model

Health state	Absolute utility	Source	Utility decrement
Progression free	0.75	Lenvatinib NICE submission[12]	0.26
Progressed	0.68	Lenvatinib NICE submission[12]	0.32

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TABLE 65 Drug acquisition costs: BTG CTT-ineligible model

Item	Unit cost	Source
Treatment and aftercare costs		
TheraSphere	£8000.00	Clinician informed
QuiremSpheres	£8000.00	Assumed the same as TheraSphere
SIR-Spheres	£8000.00	NICE Medtech Innovation Briefing[188]
Sorafenib	£3576.56	NICE BNF[115]
Lenvatinib	£1437.00	
Regorafenib	£3744.00	
BSC	£0.00	Assumed

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TABLE 66 Health state costs and one-off progression costs: BTG CTT-ineligible model

Item	Unit cost	Cost per cycle	
		Progression free	Progressed
Physician visits			
Oncologist	£166.85	£115.51	£58.53
Hepatologist	£262.40	£41.18	£121.11
Macmillan nurse	£42.00	£19.38	£38.77
Gastroenterologist	£146.29	£10.80	£0.00
Radiologist	£152.27	£11.24	£0.00
Clinical nurse specialist	£42.00	£19.38	£9.69
Palliative care physician/care	£42.00	£5.04	£29.08
Laboratory tests			
Full blood count	£2.32	£1.61	£1.07
Liver function tests	£20.07	£6.21	£4.63
Alpha fetoprotein test	£20.07	£11.53	£7.04
INR	£2.32	£0.72	£0.00
Biochemistry	£1.11	£0.51	£0.26
Endoscopy	£499.51	£38.04	£0.00
Radiological tests			
CT scan	£103.95	£23.12	£27.32
MRI scan	£145.56	£12.42	£18.81
Hospitalisation			
Hospitalisation	£1928.00	£130.99	£341.70
Hospital follow-ups			
Hepatologist	£262.40	£60.55	£262.40
GP	£37.00	£51.23	£37.00
Clinical nurse specialist	£42.00	£67.85	£42.00
Total cycle costs		£627.31	£999.40

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TABLE 67 One-off progression costs: BTG CTT-ineligible model

Resource item	Mean cost
Physician visits	£0.00
Laboratory tests	£82.86
Radiological tests	£12.46
Hospitalisation	£0.00
Hospital follow-ups	£0.00
Total	£95.32

Adapted with permission from BTG Ltd.[103]

TABLE 68 Treatment-related AE costs: BTG CTT-ineligible model

Intervention	Total AE cost
TheraSphere	£88.65
SIR-Spheres	£111.33
QuiremSpheres	£111.33
cTACE	£112.07
DEB-TACE	£5.59
TAE	£483.88
Sorafenib	£384.15
Lenvatinib	£502.93
Regorafenib	£559.69

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Appendix 16 Model parameters and plots independent economic assessment

TABLE 69 Proportion of patients downstaged to curative therapy

Population	After SIR-Spheres	After sorafenib
Base case (whole population)		
Liver transplant	1.09%	0.46%
Resection	1.63%	0.00%
Ablation	3.26%	0.92%
Low tumour burden and ALBI 1		
Liver transplant	2.25%	0.70%
Resection	4.50%	0.00%
Ablation	7.87%	1.40%

TABLE 70 Adverse event rates

Grade 3/4 AEs (significant/ ≥ 5% of patients)	Rate (%)				
	SIR-Spheres	TheraSphere	QuiremSpheres	Sorafenib	Lenvatinib
Abdominal pain	3.0	3.0	3.0	6.0	0.0
Alopecia	0.0	0.0	0.0	0.0	0.0
Anaemia	0.0	0.0	0.0	0.0	0.0
Anorexia	3.0	3.0	3.0	5.0	0.0
Ascites	0.0	0.0	0.0	0.0	0.0
Aspartate aminotransferase level increase	0.0	0.0	0.0	0.0	5.0
Blood bilirubin level increase	4.0	4.0	4.0	4.0	6.5
Cardiac failure, congestive	1.0	1.0	1.0	5.0	0.0
Diarrhoea	1.0	1.0	1.0	14.0	4.2
Fatigue	9.0	9.0	9.0	19.0	3.8
Gamma-glutamyltransferase level increase	0.0	0.0	0.0	0.0	5.5
Haematological biological abnormalities	10.0	10.0	10.0	13.0	0.0
Haemorrhage	0.0	0.0	0.0	0.0	0.0
Hypophosphataemia	0.0	0.0	0.0	0.0	0.0
Hand–foot skin reaction	0.0	0.0	0.0	6.0	2.9
Hypertension	0.0	0.0	0.0	2.0	23.3
Liver dysfunction	8.0	8.0	8.0	13.0	0.0
Nausea/vomiting	0.0	0.0	0.0	0.0	0.0

continued

TABLE 70 Adverse event rates (*continued*)

Grade 3/4 AEs (significant/ ≥ 5% of patients)	Rate (%)				
	SIR-Spheres	TheraSphere	QuiremSpheres	Sorafenib	Lenvatinib
Other increased liver values	9.0	9.0	9.0	7.0	0.0
Platelet count decreased	0.0	0.0	0.0	0.0	5.5
Proteinuria	1.0	1.0	1.0	4.0	5.7
Rash/desquamation	0.0	0.0	0.0	0.0	0.0
Weight loss	0.0	0.0	0.0	3.0	7.6
Cholecystitis	0.0	0.0	0.0	0.0	0.0
Hepatic encephalopathy	0.0	0.0	0.0	0.0	0.0

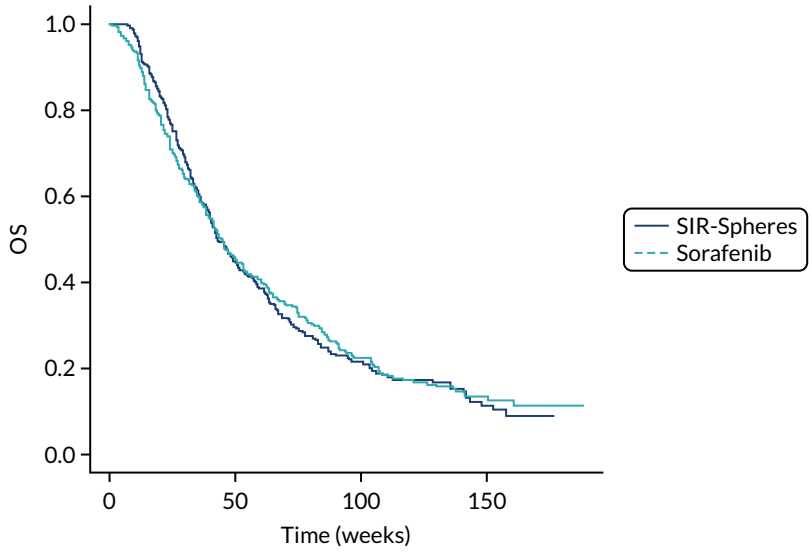

FIGURE 26 Kaplan–Meier plot of OS, for SIR-Spheres and sorafenib, from the pooled SARAH and SIRveNIB data set.

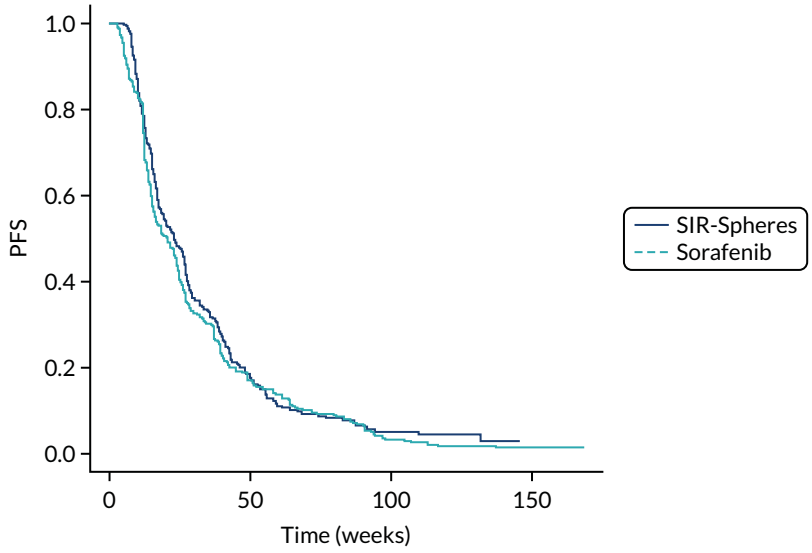

FIGURE 27 Kaplan–Meier plot of PFS, for SIR-Spheres and sorafenib, from the pooled SARAH and SIRveNIB data set.

TABLE 71 Summary of observed survival estimates for SIR-Spheres and sorafenib, from the SARAH and SIRveNIB pooled data set

Survival	SIR-Spheres	Sorafenib
OS (weeks)		
Median (95% CI)	42.86 (39.86 to 51.14)	44.38 (40.68 to 50.82)
Interquartile range	26.43–84.00	21.99–90.96
PFS (weeks)		
Median (95% CI)	22.99 (19.00 to 26.77)	20.52 (16.29 to 23.73)
Interquartile range	12.76–41.14	12.09–39.49

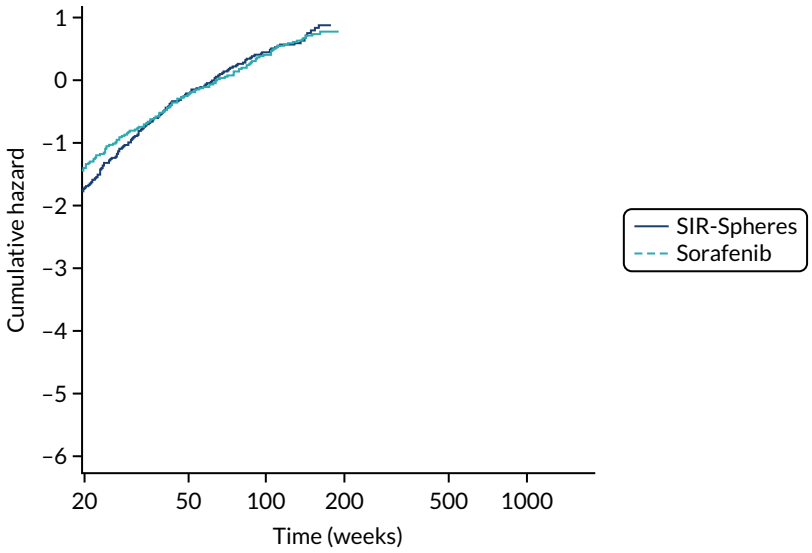

FIGURE 28 Log-cumulative hazard plot of OS, for SIR-Spheres and sorafenib, from the pooled SARAH and SIRveNIB data set.

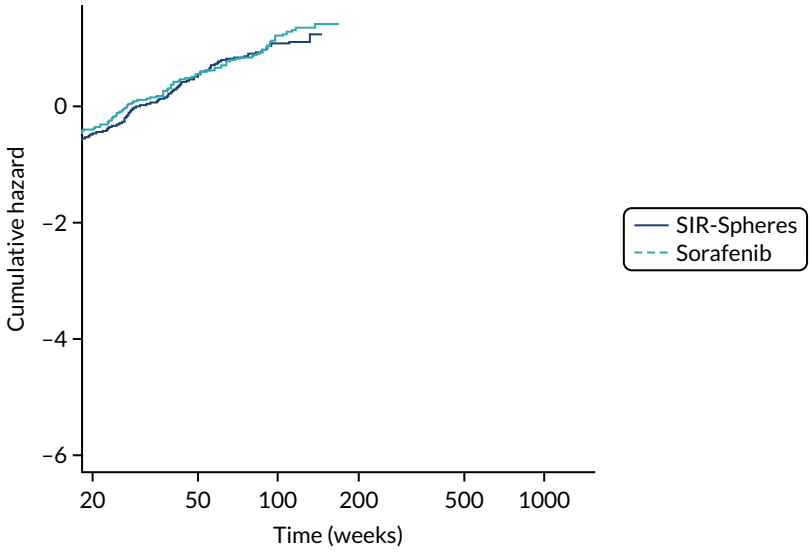

FIGURE 29 Log-cumulative hazard plot of PFS, for SIR-Spheres and sorafenib, from the pooled SARAH and SIRveNIB data set.

TABLE 72 Akaike information criterion and BIC: OS for SIR-Spheres and sorafenib, from the pooled SARAH and SIRveNIB data set (survival analysis conducted by the AG)

	SIR-Spheres		Sorafenib	
Model	AIC	BIC	AIC	BIC
Generalised gamma	2343.50	2354.54	3146.87	3158.84
Weibull	2394.10	2401.46	3168.12	3176.10
Exponential	2412.02	2415.70	3173.08	3177.08
Log-logistic	2357.55	2364.91	3144.28	3152.26
Log-normal	2350.14	2357.50	3146.02	3154.00
Gompertz	2412.72	2420.08	3175.06	3183.04

TABLE 73 Akaike information criterion and BIC: PFS for SIR-Spheres and sorafenib, from the pooled SARAH and SIRveNIB data set

	SIR-Spheres		Sorafenib	
Model	AIC	BIC	AIC	BIC
Generalised gamma	2225.88	2236.91	3120.26	3132.24
Weibull	2312.97	2320.33	3182.16	3190.15
Exponential	2337.34	2341.02	3195.35	3199.34
Log-logistic	2254.74	2262.10	3129.63	3137.61
Log-normal	2245.68	2253.04	3120.23	3128.21
Gompertz	2338.53	2345.89	3197.35	3205.33

TABLE 74 Fit statistics for the survival analyses of SARAH data (conducted by Sirtex)

	PFS		OS	
Model	AIC	BIC	AIC	BIC
Per-protocol population (SARAH[19] only)				
Log-normal	1881.7	1897.4	2181.2	2196.8
Exponential	1977.8	1985.6	2233.6	2241.4
Weibull	1953.4	1969	2213.8	2229.4
Generalised gamma	1874.7	1898.1	2183.9	2207.3
Gompertz	1976.3	1991.9	2231.3	2246.9
Log-logistic	1895.1	1910.8	2190	2205.6

TABLE 74 Fit statistics for the survival analyses of SARAH data (conducted by Sirtex) (*continued*)

	PFS		OS	
Model	**AIC**	**BIC**	**AIC**	**BIC**
Low tumour burden and ALBI 1 subgroup				
Log-normal	386.3	395.4	427.6	436.7
Exponential	394.4	398.9	442.6	447.1
Weibull	393.8	402.9	429.6	438.7
Generalised gamma	389.3	403	431.3	445
Gompertz	397.4	406.5	435.2	444.3
Log-logistic	389.4	398.5	428.4	437.5
No macrovascular invasion subgroup				
Log-normal	783.4	795.3	846.2	858.1
Exponential	815.5	821.4	872.6	878.6
Weibull	805.6	817.6	855	866.9
Generalised gamma	786.2	804.1	848.8	866.7
Gompertz	817.1	829	866.8	878.8
Log-logistic	789.5	801.5	848.7	860.6

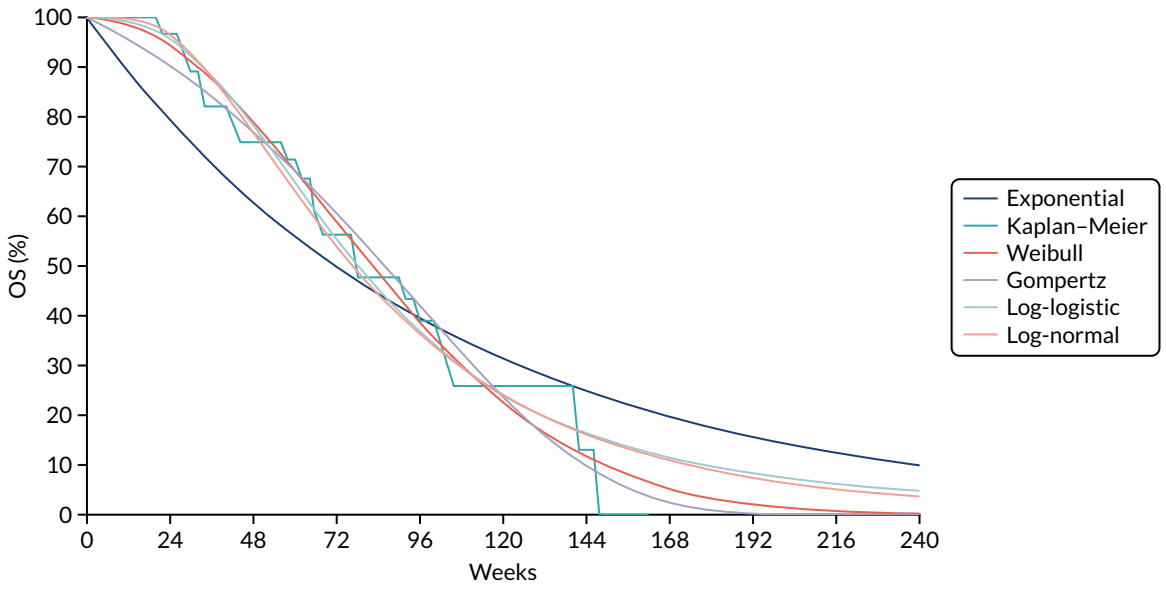

FIGURE 30 Extrapolation of OS: low tumour burden and ALBI 1 subgroup – SIR-Spheres.

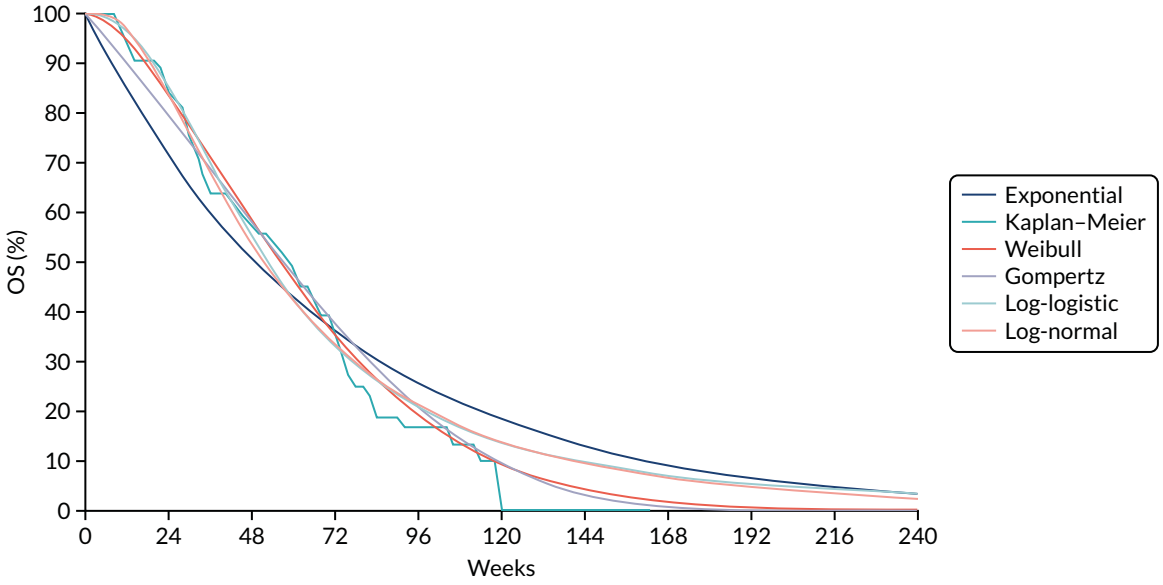

FIGURE 31 Extrapolation of OS: no-MVI subgroup – SIR-Spheres.

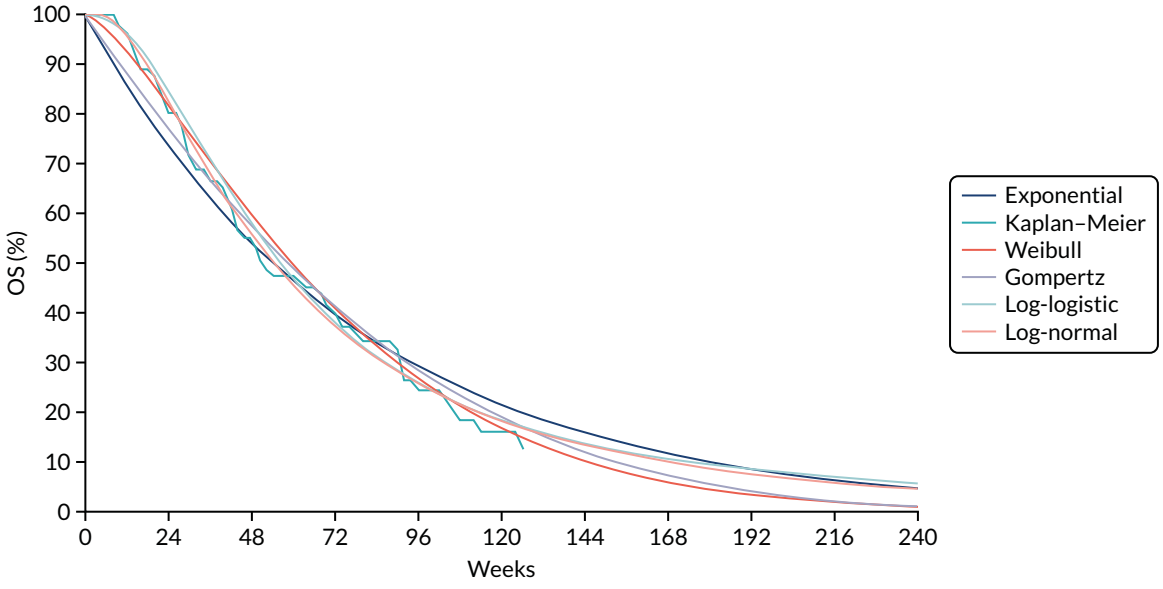

FIGURE 32 Extrapolation of OS: low tumour burden and ALBI 1 subgroup – sorafenib.

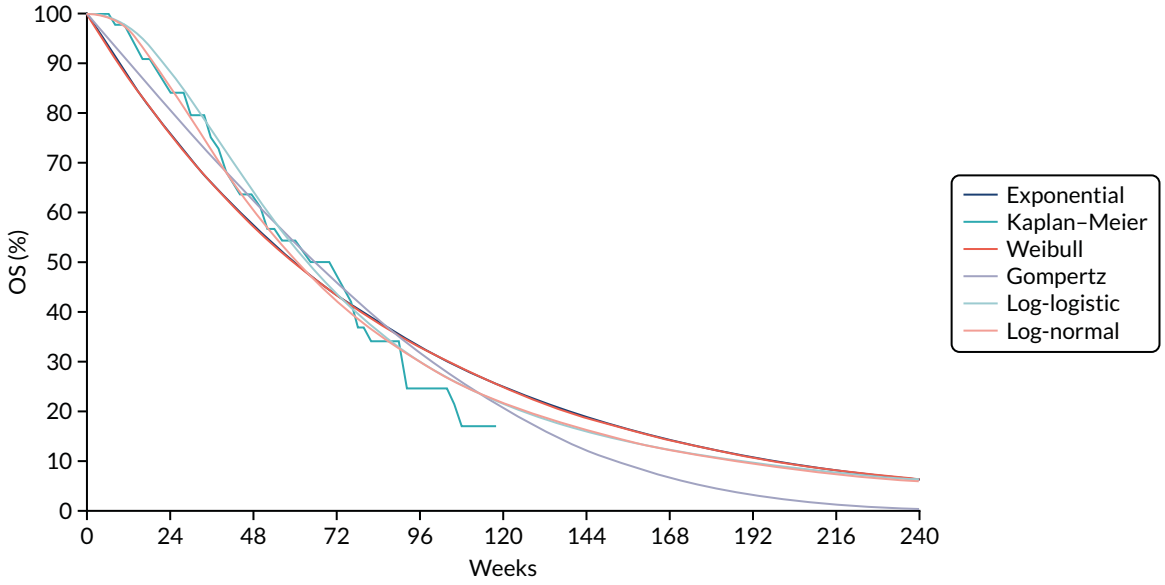

FIGURE 33 Extrapolation of OS: no-MVI subgroup – sorafenib.

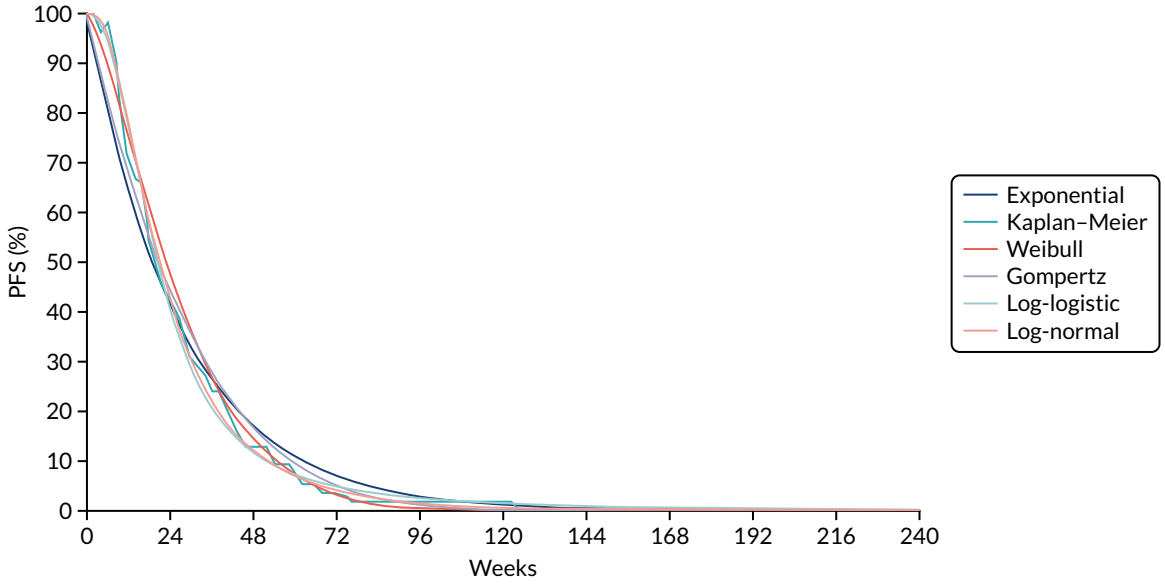

FIGURE 34 Extrapolation of PFS: low tumour burden and ALBI 1 subgroup – SIR-Spheres.

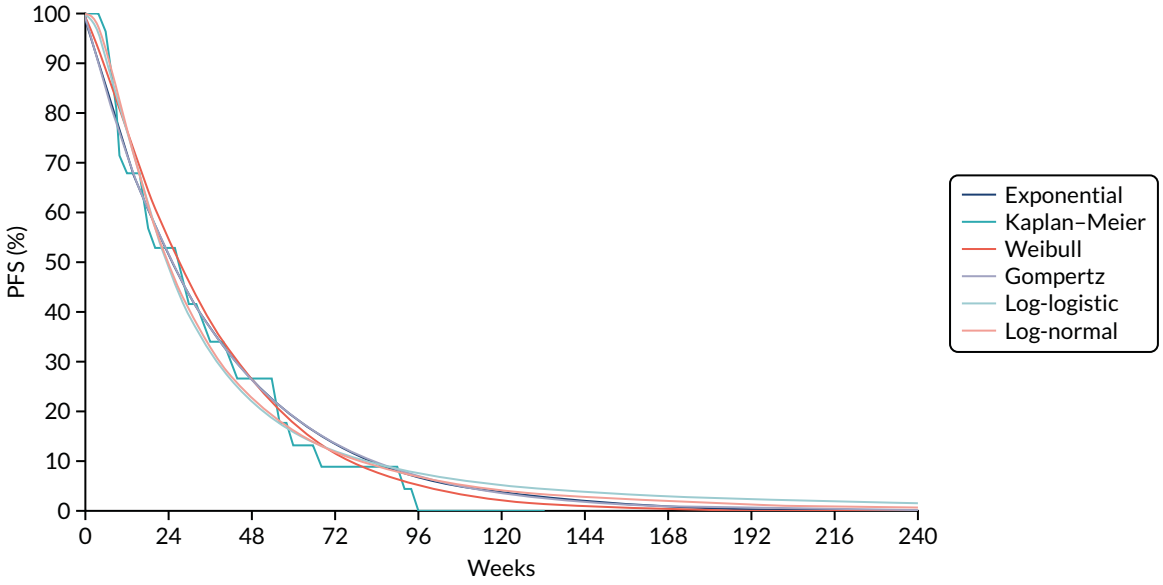

FIGURE 35 Extrapolation of PFS: no-MVI subgroup – SIR-Spheres.

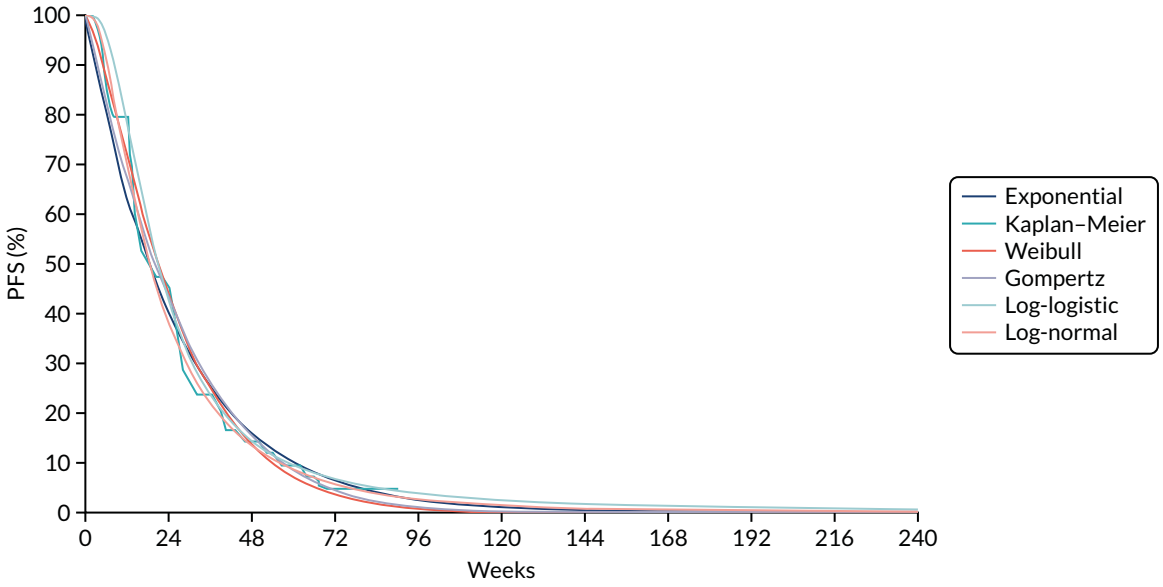

FIGURE 36 Extrapolation of PFS: low tumour burden and ALBI 1 subgroup – sorafenib.

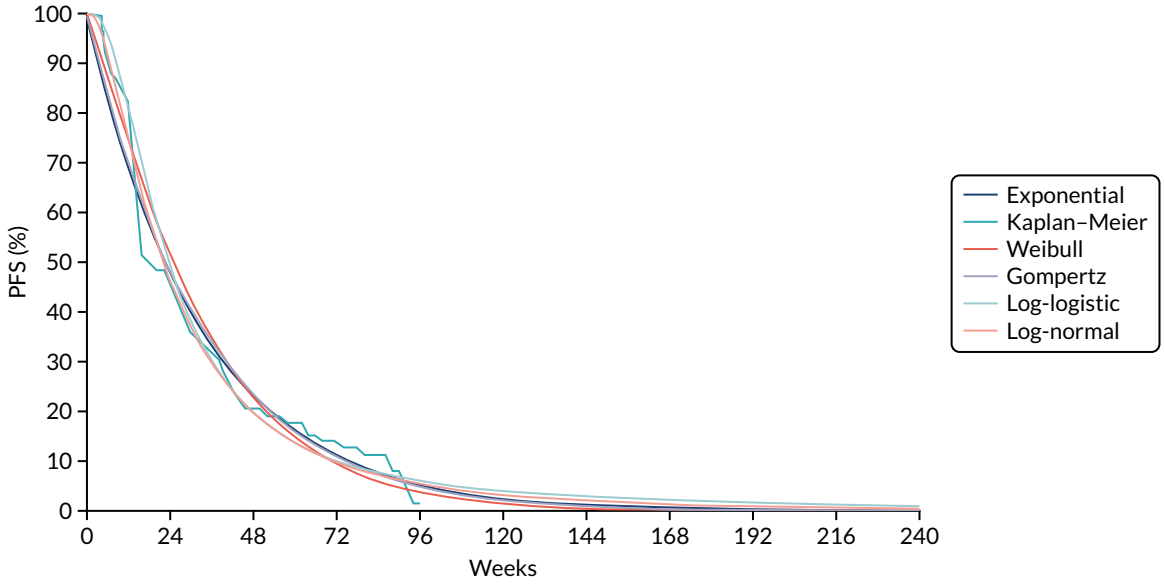

FIGURE 37 Extrapolation of PFS: no-MVI subgroup – sorafenib.

TABLE 75 Adverse event unit costs

AE	Unit cost per episode	Source
Abdominal pain	£42.19	Sirtex submission[102] (inflated from TA474[11])
Alopecia	£18.59	Sirtex submission[102] (inflated from TA474[11])
Anaemia	£615.76	*National Schedule of Reference Costs 2017–2018*[107] (hospitalisation) (TA535[154])
Anorexia	£657.86	Sirtex submission[102] (inflated from TA535[154])
Ascites	£615.76	*National Schedule of Reference Costs 2017–2018*[107] (hospitalisation) (TA535[154])
Aspartate aminotransferase level increase	£634.50	Sirtex submission[102] (inflated from TA551[124])
Blood bilirubin level increase	£916.47	Sirtex submission[102] (inflated from TA535[154])
Cardiac failure, congestive	£1979.71	*National Schedule of Reference Costs 2017–2018*[107]
Diarrhoea	£605.13	Sirtex submission[102] (inflated from TA551[124])
Fatigue	£677.68	Sirtex submission[102] (inflated from TA551[124])
Gamma-glutamyltransferase level increase	£634.50	Sirtex submission[102] (inflated from TA551[124])
Haematological biological abnormalities	£1713.98	Assumed same as anaemia (TA514[13])
Haemorrhage	£0.00	Sirtex submission[102] (TA474[11])
Hypophosphataemia	£1297.52	Sirtex submission[102] (inflated from TA551[124])
Palmar–plantar erythrodysesthesia syndrome	£897.98	Sirtex submission[102] (inflated from TA535[154])
Hypertension	£888.12	Sirtex submission[102] (inflated from TA551[124])
Liver dysfunction	£1207.13	Sirtex submission[102] (inflated from TA535[154])
Nausea/vomiting	£82.18	*National Schedule of Reference Costs 2017–2018*[107] (hospitalisation) (TA535[154])
Other increased liver values	£634.50	Sirtex submission[102] (inflated from TA551[124])
Platelet count decrease	£634.50	Sirtex submission[102] (inflated from TA551[124])
Proteinuria	£812.04	Sirtex submission[102] (inflated from TA551[124])
Rash/desquamation	£71.09	Sirtex submission[102] (inflated from TA474[11])
Weight loss	£665.35	Sirtex submission[102] (inflated from TA551[124])

Appendix 17 Confidential information has been removed

Confidential information has been removed.

EME
HS&DR
HTA
PGfAR
PHR

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